UNITED STATES DISTRICT COURT
DISTRICT OF NEVADA
BEFORE THE HONORABLE MIRANDA DU, DISTRICT JUDGE
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AMARIN PHARMA, INC., and AMARIN PHARMACEUTICALS IRELAND LIMITED, Plaintiffs, -vs- HIKMA PHARMACEUTICALS USA INC., et al., Defendants.	No. 2:16-cv-02525-MMD-NJK January 27, 2020 Reno, Nevada Volume 6

TRANSCRIPT OF BENCH TRIAL

APPEARANCES:

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Reported by: Kathyrn M. French, CCR #392, RPR
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US District Court
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(Appearances continue on next page.)

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08:37:38

RENO, NEVADA, MONDAY, JANUARY 27, 2020, 8:30 A.M.

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THE COURT: Good morning, please be seated.

Good morning, counsel. You ready to proceed with plaintiffs' next witness?

MR. ELIKAN: Yes, Your Honor. This is Jeffrey Elikan on behalf of Amarin, and we call Dr. Peter Toth.

PETER PAUL TOTH, M.D.,
called as a witness on behalf of the Plaintiffs,
was sworn and testified as follows:

THE CLERK: Please be seated.

Please state your full name and spell your last name.

THE WITNESS: My full name is Peter Paul Toth, T-o-t-h.

THE CLERK: Thank you.

MR. ELIKAN: May I proceed, Your Honor?

THE COURT: Yes.

DIRECT EXAMINATION

BY MR. ELIKAN:

Q Good morning. Could you state your name for the record.

A Peter Paul Toth.

Q Are you currently employed?

A Yes, sir.

Q And where are you employed?

08:31:46 A **At the Community General Hospital Medical Center in Sterling, Illinois.**

08:31:51 Q **Can you tell us a little bit about the hospital.**

08:31:52 A **Sure. It's a 160-bed hospital. It's in Sterling, Illinois, which is in northwestern Illinois, and it also has a variety of satellite clinics to serve different communities.**

08:31:54 Q **What's your current position there at CGH?**

08:32:05 A **I'm the Director of Preventive Cardiology. I'm also on staff as a primary care physician.**

08:32:09 Q **And how long have you held the position of Director of Preventive Cardiology at CGH?**

08:32:14 A **Approximately ten years.**

08:32:17 Q **What are you duties and responsibilities in that role?**

08:32:20 A **Well, my role is to make sure that the care of patients who have risk factors for cardiovascular disease is kept up-to-date, and so I provide physicians periodic updates on guidelines and I'm also a resources for other people to reach out to.**

08:32:23 Q **Do you also see patients?**

08:32:27 A **Yes, counsel.**

08:32:29 Q **And on average, how many patients do you see per month?**

08:32:32 A **I see between 4 and 500 and last year in the year 2019, I managed 500 -- excuse me, 5,143 patient visits.**

08:32:36 Q **And for how long have you treated patients?**

08:32:41 A **I'm in my 24th year of practice.**

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08:33:18 Q **And you've been seeing patients continuously during that**
08:33:21 **time?**
08:33:21 A **Yes, counsel.**
08:33:22 Q **How did you become involved in the field of preventive**
08:33:26 **cardiology?**
08:33:26 A **Well, it was an area that drew me very strongly. It's an**
08:33:31 **area where you can make a big difference in terms of patient**
08:33:36 **outcomes, in terms of helping to maintain quality of life and**
08:33:42 **preventing cardiovascular morbidity and mortality, and it's**
08:33:48 **something I feel very passionate about.**
08:33:49 Q **And what percentage of the patients that you see present**
08:33:53 **with cardiovascular issues?**
08:33:56 A **Seventy-five to 80 percent.**
08:33:57 Q **Now, this case involves hypertriglyceridemia or -- and**
08:34:03 **specifically severe hypertriglyceridemia. Do you treat**
08:34:06 **patients with hypertriglyceridemia?**
08:34:08 A **Yes, counsel.**
08:34:09 Q **And do you treat patients with severe**
08:34:12 **hypertriglyceridemia?**
08:34:12 A **I do.**
08:34:13 Q **And for how long have you treated patients with those**
08:34:19 **conditions?**
08:34:19 A **Since I've been in practice.**
08:34:21 Q **Can you estimate, over the course of your career, how**
08:34:28 **many patients you've treated with severe hypertriglyceridemia?**

08:34:33 A It would be in the hundreds.

08:34:37 Q I want to talk more about your qualifications now.

08:34:40 Can you please --

08:34:42 MR. ELIKAN: Can we please turn to PX 1172. And Dr. Toth it's in your binder I'll be showing you things on the

08:34:45 screen as well.

08:34:50 THE WITNESS: Thank you.

08:34:51 BY MR. ELIKAN:

08:34:51 Q Do you recognize this document?

08:34:51 A Yes, sir, it's my curriculum vitae.

08:34:52 Q Does it accurately set forth your education, training,

08:34:56 and experience?

08:34:59 A Yes.

08:35:00 MR. ELIKAN: Your Honor, we move for admission

08:35:02 PX 1172.

08:35:05 MR. KLEIN: No objection.

08:35:06 THE COURT: PX 1172 is admitted.

08:35:06 (Plaintiffs' Exhibit 1172 received in evidence.)

08:35:06 BY MR. ELIKAN:

08:35:12 Q In addition to your CV have you had the opportunity to

08:35:12 assist in preparing the slides that illustrate aspects of your

08:35:15 professional background as well as other testimony you'll be

08:35:15 offering today?

08:35:23 A Yes, counsel.

08:35:23 Q In addition to your position at CGH medical center do you

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hold any positions in medical schools?

A Yes.

MR. ELIKAN: Can we have PDX 6-2, Mr. Brooks.

BY MR. ELIKAN:

Q What are those positions?

A I am a professor of clinical family and community medicine in the department of family and community medicine at the University Illinois School of Medicine in Peoria, Illinois.

I am also a professor of clinical medicine in the Department of Medicine, Division of Cardiology Michigan State University, College of Osteopathic Medicine, in East Lansing, Michigan.

And I'm also an adjunct associate professor of Medicine in the Department of Medicine, Division of Cardiology at the Ciccarone, and I'll spell that for the court reporter, C-i-c-c-a-r-o-n-e, Center for the Prevention of Cardiovascular Disease at the Johns Hopkins University School of Medicine in Baltimore, Maryland.

Q Can you briefly describe your role or your position as a professor of clinical family and community medicine at Michigan State.

A At Michigan State University --

Q I'm sorry at the University of Illinois School of Medicine.

08:36:40 A **Sure. It is my role to teach medical students. Medical**
08:36:45 **students come to my clinic and shadow me and I instruct them**
08:36:48 **about how primary care medicine works. They are also**
08:36:52 **introduced not preventive cardiology. And so medical students**
08:36:59 **shadow me, meaning they're with me for weeks at a time.**
08:37:02 Q **And at Michigan State, what do you do there?**
08:37:05 A **Yes. I participate in continuing medical education, and**
08:37:11 **I have also been asked to co develop a new textbook on**
08:37:16 **cardiovascular pathophysiology with the division chief of**
08:37:21 **cardiology.**
08:37:22 Q **And can you briefly describe your position at Johns**
08:37:28 **Hopkins.**
08:37:28 A **Yes. It's a collaborative position where we engage in a**
08:37:33 **great deal of research and part of my role in addition to**
08:37:37 **performing research is to also mentor medical students and**
08:37:42 **cardiology fellows in being able to synthesize data, prepare**
08:37:46 **manuscripts, submit them to journals, attend conferences and I**
08:37:51 **mentor them in performing that type of research, clinical**
08:37:55 **research.**
08:37:55 Q **And are your roles at Hopkins and at Michigan State**
08:38:06 **focused on cardiovascular prevention issues?**
08:38:06 A **Yes.**
08:38:06 Q **I want to talk a little bit with your involvement in**
08:38:12 **professional organizations now. Have you held leadership**
08:38:14 **positions in any professional organizations?**

A **Yes, counsel.**

Q **I want to look at page 1 of your CV. At number four.**

It states that you're president elect American Society of Preventive Cardiology 2018 to 2020.

What is the American Society of Preventive Cardiology?

A **The American Society of Preventive Cardiology is an association of healthcare professionals who are committed to preventive cardiology.**

Q **About how many members are there?**

A **I believe about 2000.**

Q **And moving -- an item down I see that you're listed as past president National Lipid Association, 2013, 2014. What is the National Lipid Association?**

A **The National Lipid Association is an association of healthcare professionals who are committed to the treatment of dyslipidemia.**

Q **Then looking at item 7, past president American Board of Clinical Lipidology, what is the American Board of Clinical Lipidology?**

A **The American Board of Clinical Lipidology is a body that provides certification in the practice of the clinical lipidology.**

So its role is to foster a program that is comprehensive in scope in terms of continuing medical

education, but also a formal 200 questions exam that applicants must pass in order to achieve certification in clinical lipidology. And while I was president, it was my role to completely redo the exam and update the criteria for certification.

Q And by updating the criteria for certification and managing the process of certification, are you essentially acting as a gatekeeper?

A Yes.

Q Let's talk about your editorial positions. Have you held editorial positions at any scientific journals?

A Yes counsel.

MR. ELIKAN: Can we have PDX 6-3.

BY MR. ELIKAN:

Q What editorial positions have you held?

A I was I believe for three-and-a-half years, editor-in-chief of the *Journal of Applied Research and Experimental Therapeutics*.

Currently I'm editor in chief of the Contemporary Cardiology series by the publisher Springer Verlag. This is a 130-volume library of books that are subspecialized in cardiology, and it is my role to not only recruit authors but I also have to review every volume that comes in and it is my role to further develop this into a 200-book collection.

I am also co editor-in-chief of the Archives of the

Medical Science Atherosclerotic Diseases, and for five years I served as an associate editor of the Year Book of Endocrinology section on lipids, lipoproteins, atherosclerosis and coronary artery disease.

And I'm also an associate editor for the *Journal of Clinical Lipidology*.

Q Do you have experience as a peer reviewer of scientific journals?

A Yes, sir.

MR. ELIKAN: Can we have the next slide PDX 6-4.

BY MR. ELIKAN:

Q And can you highlight some of the journals to which you've served as a peer reviewer.

A Yes, *Circulation*, *Journal of the American College of Cardiology*, *Journal of Clinical Lipidology*, the *New England Journal of Medicine* and the *Lancet*.

Q Have you been involved in the conduct and administration of clinical trials?

A Yes.

Q Turning to page 7 of your CV, I want to look at the section titled clinical investigation experience.

A Yes.

Q And if we look at 7 and 8 together I see you're listed as a primary investigator in nine clinical trials is that right?

A Yes.

08:42:47 Q **And what is primary investigator.**

08:42:50 A **Well, a primary investigator would be someone who manages the clinical trial at the local level.**

08:42:55 **There are many centers around the world or in some studies just in the U.S., but typically there are numerous centers that enroll patients into the clinical trial and at each site someone is the project leader.**

08:43:10 **And at each site the primary investigator would not only assume responsibility for the appropriate conduct of the trial, but also would be responsible for the care of that patient if there was an adverse event or an adverse reaction in response to the medication that was being studied.**

08:43:28 Q **In general, in terms of subject matter, what did these nine clinical trials concern?**

08:43:36 A **They concerned management of dyslipidemia, hypertension, diabetes.**

08:43:42 Q **Cardiovascular disease?**

08:43:44 A **Yes, cardiovascular risk factors.**

08:43:47 Q **Now, item number eight that's listed here is the STRENGTH trial?**

08:43:54 A **Yes.**

08:43:55 Q **What's the STRENGTH trial?**

08:43:56 A **Well, the STRENGTH trial was a clinical trial that evaluated the efficacy of Epanova over and above statin therapy compared to a statin, and for the court reporter**

Epanova is E-p-a-n-o-v-a and that trial was recently terminated.

Q And what's the active ingredient in Epanova or ingredients?

A It would be a formulation of EPA and DHA. And if I may, counsel, with the Court's permission, instead of always saying icosapentaenoic add and docosahexaenoic acid, would it be permissible for me to just say EPA and DHA.

THE COURT: I think that's entirely permissible. We've been using other acronyms as well. Thank you.

THE WITNESS: Thank you, Your Honor.

BY MR. ELIKAN:

Q Does it contain other omega-3 fatty acids or just EPA and DHA?

A Yes, it's virtually impossible to purify these down to 100 percent purity.

Q And you said it's been terminated. Do you have an understanding as to why it's been terminated?

MR. KLEIN: Objection. Beyond the scope of the report, Your Honor.

THE COURT: Counsel?

MR. ELIKAN: Your Honor, it was just terminated recently. It's listed as a current clinical trial in his CV. He just said it was terminated. It seems to me it's just recent events of the last few weeks and it just seems

informative on background.

MR. KLEIN: I have no objection to him saying it was terminated but I have no idea what answer is coming. We've had no notice that there was going to be any discussion as to why it was terminated.

THE COURT: And Mr. Elikan, I sympathize with Mr. Klein's objection because they -- he would have no way of verifying the answer because there's no background information that he's aware of relating to the termination. And I'm not sure it's that relevant so --

MR. ELIKAN: I can move on, Your Honor.

THE COURT: All right. The objection is sustained.

BY MR. ELIKAN:

Q **Are you author of any publication in the field -- publications in the field of lipidology and in the field of cardiovascular disease prevention?**

A **Yes, counsel.**

Q **I want to turn to page -- to the section in your CV addressing publications. And am I correct that that bridges from the bottom of page 11 to page 70?**

A **Yes.**

Q **How many total publications do you have?**

A **I have 14 textbooks addressing -- there are two that address preventive cardiology, and then there are multiple,**

but there's two volume work on hypertension, multiple works on dyslipidemia. There's another one on glucolipotoxicity toxicity in the heart. I'm sorry Madam court reporter I'll spell that for you. G-l-u-c-o-l-i-p-o-t-o-x-i-c-i-t-y.

Then there's also a text book on diabetes. There are 14 -- there are two more books coming later this year. One called *Therapeutic Lipidology* and the other one called the *Preventive Cardiology Handbook*.

I have 376 published papers, nearly 300 published abstracts, 77 book chapters.

Q Was that a -- I lost track of the math but it seemed like we were around 700 or thereabouts. What's your best estimate?

A Yes, sir, that's fine.

Q In general terms, what do these publications all of them together, generally concern?

A They concern different facets of either cardiovascular disease prevention or established cardiovascular disease. They can address lipids, diabetes, hypertension, metabolic syndrome. The range is wide.

Q And do you consult with pharmaceutical companies?

A Yes, sir.

Q I don't need an exhaustive list but what are some of the pharmaceutical companies with which you've consulted?

A Amarin, Amgen, Merck, Regenera.

Q And in general terms what does your consulting work

involve?

A It involves performing research. It involves speaking. There are specific pharmaceutical drugs that I have also lectured on. And it's pretty much a balance between the two.

Q Why do you choose to do consulting work with pharmaceutical companies?

A Because I think it's obviously extremely important to advance medical science, and they need to partner with physicians who are committed to research. If we don't do research, nothing is going to move forward.

And progress in medicine is tantamount in being able to deliver good effective medical care. And patients are willing to participate in clinical trials because they understand that as well.

Q Okay. And the speaking engagements, why do you choose to speak about drugs for pharmaceutical companies?

A Because I love teaching. I love teaching my peers. And it's extremely important that they be provided with up to date accurate information on what these medications do and how they are best applied in everyday medical care.

Q Let's turn to your educational background. Where did you receive your medical training?

A I went to medical school at the Wayne State University School of Medicine in Detroit, Michigan, and I did my residency training at the University of Iowa, hospitals and

clinic. I did two years in obstetrics and gynecology and two years in family medicine.

Q And where did you receive your undergraduate degree and in what discipline did you major?

A I received my undergraduate degree at Princeton University in Princeton, New Jersey, in biochemistry.

Q Did you get a further degree aside from medical school another graduate degree?

A Yes, sir. I have a doctorate in biochemistry from Michigan State University in East Lansing, Michigan.

MR. ELIKAN: Your Honor, we offer Dr. Toth as an expert in lipidology, the treatment of hypertriglyceridemia, including severe hypertriglyceridemia and the prevention and treatment of cardiovascular disease.

MR. KLEIN: No objection.

THE COURT: The request to certify Dr. Toth as an expert in those three areas is granted.

MR. ELIKAN: Thank you, Your Honor.

BY MR. ELIKAN:

Q We'll be talking about Vascepa today. Is that a drugs that you prescribe?

A Yes.

Q In your opinion, is it an important addition to the armamentarium, the treatments available for physicians to treat hypertriglyceridemia?

A **Yes, counsel.**

Q **And why?**

A **Because it's solved a very important problem in clinical lipidology and cardiovascular medicine, namely, that it is a medication that can be used in patients with severe hypertriglyceridemia to lower triglycerides without raising the LDL cholesterol or the so-called bad cholesterol.**

Q **Did review Dr. Heinecke's testimony?**

A **I did.**

Q **Do you recall that Dr. Heinecke testified that the asserted claims would have been obvious to a person of ordinary skill in the art in March of 2008?**

A **Yes.**

Q **Do you agree with him?**

A **No, sir.**

Q **Now, before we get further into the substance of your opinion that the asserted claims would not have been obvious, I want to touch upon some scientific background issues.**

MR. ELIKAN: Can we have PDX 6-5, Mr. Brooks.

BY MR. ELIKAN:

Q **Can you explain what PDX 6-5 shows.**

A **Yes, counsel. This is a schematic that summarizes the metabolism of lipoproteins, namely the conversion of VLDL or very low density lipoproteins to LDL or low density lipoproteins.**

If we go all the way to the left, under number one, we see that the VLDL particles which are highly enriched in triglyceride are produced and secreted by the liver into the bloodstream.

Now, this is very important because the VLDL particles are enriched with triglyceride and cholesterol and it is the role of these particles to distribute stored energy to various cells of the body.

Think of the triglyceride as something of a gasoline that can be combusted in the engine of a vehicle, which in the case of the cell, would be the mitochondria.

The triglycerides can't be transported in blood by themselves because they're fats and fats do not dissolve in water. Oil and water don't mix. The lipoprotein is able to carry these triglycerides and cholesterol through the blood and get them to the cells that need this form of stored energy.

Q **So they basically act like -- you analgized to gas before in saying the triglyceride are like gas, and the lipoproteins the gas truck.**

A **Yes, that is a very apt analogy.**

Q **And can you explain what the squiggly lines and dots are in 2.**

A **Yes, the squiggly lines in red represent triglycerides and the yellow globules represent cholesterol of course highly**

schematically.

So these VLDL particles are in the blood after they're secreted, and as we move to number 3, the triglycerides have to be removed so that they can be processed by cells. And there's an enzyme in the body called lipoprotein lipase and that's l-i-p-o-p-r-o-t-e-i-n new word l-i-p-a-s-e.

This enzyme removes the triglycerides and facilitates their breakdown into their constituent fatty acids. The fatty acids can be burned as fuel and they drive intermediary metabolism.

Now, what happens here as the triglycerides are removed, the particle gets smaller and the large VLDL particle under number 2 becomes and IDL particle in number 3.

Q **What does that stand for?**

A **Intermediate density lipoprotein. This is still relatively enriched with triglyceride as you can see, but as more and more of the triglyceride is removed, the particle becomes yet smaller.**

And under 4 this is an LDL particle, the low density lipoprotein particle, and this is a particle that is the so-called bad cholesterol. It carries cholesterol, but this LDL, if it's not cleared, can also wind up in blood vessel walls leading to the development of atherosclerotic disease or hardening of the arteries.

08:55:54 Q **And this whole process a metabolism of lipoproteins?**

08:55:57 A **Yes, this is a high schematic of lipoprotein physiology. As the triglyceride enriched lipoprotein is progressively converted into a triglyceride depleted lipoprotein leading to the formation of LDL.**

08:56:14 Q **And all things being equal, as the VLDL particles change and become IDL and then LDL, how does that impact how much LDL or low density lipoprotein cholesterol is present in the blood?**

08:56:31 A **Well, if there's a large backlog of this VLDL say because someone has a logjam, they don't express lipoprotein lipase appropriately, then they have impaired capacity to drive this conversion to allow for this physiologic flow of the large VLDL down to the LDL.**

But if you break that logjam and suddenly you activate the enzyme somehow, then you can see a large surge in the production of that LDL and the LDL levels would rise.

08:57:10 Q **And what does that mean for the amount of LDL-C or LDL cholesterol in the blood?**

08:57:16 A **It increases.**

08:57:17 Q **And was all of this understood as of March 2008?**

08:57:23 A **Yes.**

08:57:24 Q **Now, we've been talking about three different lipoproteins, VLDL, IDL, LDL. Have you prepared a slide showing these three different types of lipoproteins in greater**

detail.

A **Yes, counsel.**

MR. ELIKAN: Can we have PDX 6-6.

BY MR. ELIKAN:

Q **Can you explain what is depicted PDX 6-6.**

A **Yes. This schematic demonstrates very nicely that as you convert a VLDL particle to the IDL particle in the middle, you will decrease the triglyceride content of the VLDL which begins at around 55 to 80 percent, and this will decrease to approximately 20 to 50 percent.**

At the same time it becomes more cholesterol enriched going from 5 to 15 percent of total content up to 20 to 40 percent.

Q **Are you describing the passage from VLDL to IDL right now?**

A **Yes.**

Q **Okay. Can you walk us through the LDL.**

A **Yes. So as we go from IDL to LDL, there is even more reduction of triglyceride content within the core of the particle and the cholesterol becomes even more enriched within the core of that particle.**

Q **And what levels of triglycerides and cholesterol are present in the low density lipoprotein?**

A **It would be 5 to 15 percent triglyceride and 40 to 50 percent cholesterol.**

08:59:05 Q **And would all this been understood as well by the person**
08:59:09 **of ordinary skill in the art in March 2008?**
08:59:11 A **Yes, counsel.**
08:59:12 Q **Now, I want to talk about severe hypertriglyceridemia.**
08:59:15 **As of March 2008, was there a standard definition of severe**
08:59:19 **hypertriglyceridemia?**
08:59:21 A **There was.**
08:59:21 Q **What was it?**
08:59:22 A **It was based on the third adult treatment panel sponsored**
08:59:27 **by the National Heart Lung and Blood Institute of the National**
08:59:30 **Institutes of Health and this was published in 2001 and it was**
08:59:36 **published in multiple journals in 2002.**
08:59:39 Q **And my question is what was the definition.**
08:59:41 A **The definition of very high triglycerides was a**
08:59:46 **triglyceride level that was greater than or equal to**
08:59:50 **500 milligrams per deciliter.**
08:59:51 Q **And when you answered my question, you said very high**
08:59:54 **triglycerides. Is that one in the same as severe**
08:59:57 **hypertriglyceridemia?**
08:59:59 A **Yes.**
08:59:59 Q **Can I use those terms interchangeably?**
09:00:07 A **Yes.**
09:00:07 Q **And when I use those terms, you'll understand then that**
09:00:14 **I'm talking about someone whose fasting triglyceride levels**
09:00:19 **are at least 500 milligrams per deciliter?**

09:00:22 A **Yes.**

09:00:24 Q **Was it understood as of March 2008, that very high levels of triglycerides cause health problems?**

09:00:29 A **Yes.**

09:00:32 Q **What types of health problems?**

09:00:32 A **There were two principle health problems. The first and foremost one was the heightened risk of developing pancreatitis. Pancreatitis is an acute inflammatory condition of the pancreas.**

09:00:34 **The pancreas is a vital organ, it's located behind your stomach, and it's role is to produce digestive enzymes that are secreted into the gastrointestinal tract, but importantly the pancreas plays a critical role in regulating glucose metabolism because it also is responsible for producing insulin and glucagon.**

09:00:38 **In the setting of severe hypertriglyceridemia inflammatory changes an occur within the pancreas that can lead to sudden devastating injury to the pancreas leading to the dissolution of pancreatic tissue resulting in severe pain, inability to eat, to drink, and it constitutes a medical emergency. But even more importantly in some cases it request even result in death.**

09:00:42 **The second potential complication of severe hypertriglyceridemia is heightened risk for the development os atherosclerotic disease, cardiovascular disease.**

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09:01:57 **MR. ELIKAN: Please turn, and you can do so in your binder or on the screen, to PX 989, the ATP III2 which is what we've been calling it. Which the parties, Your Honor, have stipulated as prior art to the asserted.**

09:02:17 **And, Your Honor, either I -- since there's a stipulation as to which documents, some of them are stipulated to as prior art, would you -- would you like me to refer to the document and the paragraph number or is it sufficient to just mention the document?**

09:02:30 **THE COURT: It's sufficient to just mention the document via the exhibit number.**

09:02:35 **MR. ELIKAN: Okay. It's 324 is the joint stipulations of fact in which the stipulations are contained.**

09:02:41 **THE COURT: Yes, what I mean is I realize this is a stipulated document, you can just refer to the exhibit when you reference the document.**

09:02:49 **MR. ELIKAN: Okay. I understand but this is going to different issue, Your Honor.**

09:02:51 **There's stipulation as to certain articles that they constitute prior art and that's what I'm asking Your Honor is whether I ought to recite the paragraph and the document which those occur or is it sufficient for me to just say that it's the subject of a stipulation as prior art.**

09:03:09 **THE COURT: You could just refer to the latter that it's subject of stipulation as to the prior art.**

09:03:14 **MR. ELIKAN: Okay.**

09:03:14 **BY MR. ELIKAN:**

09:03:20 **Q Was ATP III, was this considered an authoritative text by**

09:03:25 **clinicians treating hypertriglyceridemia and severe**

09:03:29 **hypertriglyceridemia as of March 2008?**

09:03:31 **A Yes. It was a national guideline, a national standard**

09:03:35 **put together by a broad range of experts by the National**

09:03:39 **Institutes of Health.**

09:03:40 **Q Let's go to page 194, to table 7.2-4 titled "Treatment**

09:03:49 **Considerations For Elevated Serum Triglycerides."**

09:03:53 **Can you explain in general what this table concerns.**

09:03:56 **A Yes. It summarizes the triglyceride categories as well**

09:04:02 **as special treatment considerations.**

09:04:05 **Q And looking at the left-hand column, this page lists**

09:04:11 **different serum triglyceride categories, do you see that?**

09:04:14 **A I do.**

09:04:15 **Q And what were the different classifications or the**

09:04:19 **different categories of elevated serum triglycerides that were**

09:04:25 **recognized by ATP III?**

09:04:27 **A There are three; borderline high triglycerides, which**

09:04:31 **range from 150 to 199; high triglyceride, which range from 200**

09:04:37 **to 499, and very high triglycerides or severe**

09:04:44 **hypertriglyceridemia, greater than 500 milligrams per**

09:04:49 **deciliter.**

09:04:49 **Q And starting with the very high triglycerides group, what**

did ATP III state were the goals of therapy?

A There are two; number one, to reduce the triglycerides to prevent the development of acute pancreatitis, that was priority number one.

Priority number two was, once that was under control, to prevent the development of coronary heart disease.

Q So were these -- you said once it's under control. Were these considered to be goals to be pursued from the get-go, or is it a chronological thing?

A You mean were the goals to be achieved simultaneously?

Q In the ideal world?

A Well, sure. We would love to prevent everything we can, but, in the real world, getting the triglycerides down was priority number one because you wanted to make sure you did everything possible to prevent the risk of pancreatitis. Once you had that under control, then you can go ahead and chase down the risks for the coronary heart disease.

Q So that's the second priority then.

A Yes, sir.

Q And moving on to the borderline high and high groups, what did ATP III state were the goals or goal of therapy?

A For both of those groups, the primary goal was to achieve what they called the risk stratified LDL cholesterol goal.

Allow me to explain. When a patient walks through the door, if they were in primary prevention, meaning they did

not yet manifest evidence of heart disease, then you would evaluate their risk factor burden.

You would then calculate a ten-year projected risk score, which at the time was the Framingham risk score, and that would help you to determine what their level of risk was, let's say low or moderate or high.

And those different strata of risk dictated that you reduced LDL progressively more aggressively because the higher the risk, the lower the LDL that was targeted. So that's what that means.

And in secondary prevention since everyone is high risk, there was an established LDL goal.

Q So the primary goal for both according to ATP III is achieve LDL-C goal?

A Yes.

Q In March 2008, was there a physiological understanding as to why patients might suffer from severe hypertriglyceridemia?

A Yes.

MR. ELIKAN: Let's turn to page 190, to table VII.2-1, and can we highlight the title of the table, Mr. Brooks.

BY MR. ELIKAN:

Q What does this table concern?

A The classification and causes of elevated serum triglycerides.

09:08:03 Q **Okay. I want to look at the very high triglycerides portion.**

09:08:06 **Do you see that one the causes listed for very high triglycerides is familial lipoprotein lipase deficiency?**

09:08:08 A **Yes.**

09:08:12 Q **What is that?**

09:08:18 A **Familial lipoprotein lipase deficiency is a deficiency state that is genetically determined for that enzyme lipoprotein lipase that we discussed earlier. It's the enzyme that extracts and metabolizes triglycerides from the VLDL, the IDL, and there are patients who have inborn errors in the gene for that enzyme, and they either underexpress the enzyme or they express a faulty version of it and they have reduced activity of the enzyme.**

09:08:18 Q **So how does that cause very high triglycerides?**

09:08:20 A **They have inadequate capacity to convert the VLDL to IDL and then to LDL.**

09:08:27 Q **Earlier you mentioned I think a logjam?**

09:08:31 A **Yes.**

09:08:33 Q **Does that occur with somebody with this condition?**

09:08:40 A **Yes. The VLDLs, the triglycerides are increased in blood because these patients have impaired capacity to break the VLDLs and triglycerides down.**

09:08:45 Q **Do you see right underneath the entry that we've been looking at it says familial apolipoprotein C-II deficiency?**

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09:09:34 A **Yes.**

09:09:34 Q **What is that?**

09:09:35 A **Familial apo C-II deficiency is a deficiency state in apo C-II. Apo C-II is a naturally occurring activator of lipoprotein lipase.**

09:09:48 **Many enzymes have complex regulation, lipoprotein lipase is one of them. It has both intrinsic activators and inhibitors in the body and apo C-II is an activator, and when there isn't enough available because the patient underexpresses it, there may be less activity of the enzyme available to do the work of breaking the VLDL down to IDL and then LDL.**

09:10:19 **Similarly, there's another one called apo C-III overexpression which is the inhibitor of the enzyme, and then you get a functional deficiency in the enzyme.**

09:10:31 Q **Let's focus on apo C-II, I've abbreviated it. You understand though what I'm referring to?**

09:10:38 A **Yes, of course.**

09:10:38 Q **How does that in a nutshell cause very high triglycerides? If you can use an analogy like a logjam or the like that would be appreciated.**

09:10:46 A **Sure. So if the activator of the enzyme is less available, the activity of the lipoprotein lipase is reduced and there isn't enough of it to drive that conversion of VLDL to IDL and VLDL will accumulate.**

09:11:04 Q **Let's talk now about the approved treatments for severe hypertriglyceridemia available before Vascepa.**

09:11:12 **As of March 2008, what were the FDA approved treatments for very high triglycerides?**

09:11:20 A **They would have been Lovaza. It would have been fibrate drugs like fenofibrates and niacin or nicotinic acid was also approved.**

09:11:35 Q **Did these prior approved triglyceride-lowering products raise LDL-C in patients with very high triglycerides?**

09:11:44 A **They did.**

09:11:44 Q **That's true of all these treatments?**

09:11:47 A **Yes.**

09:11:48 Q **As of March 2008, did the prior art reflect that all these treatments increased LDL-C in patients with very high triglycerides?**

09:11:59 A **It did.**

09:12:00 Q **Did they reflect a substantial rise in LDL-C or simply something small-ish?**

09:12:08 A **Well, typically substantial because the rise was proportional to the magnitude of the elevation of the triglycerides.**

09:12:17 Q **As of March 2008 for how long had it been recognized that triglyceride-lowering agents could produce large LDL-C rises in patients with very high triglycerides?**

09:12:31 A **Well, depending upon the drug, anywhere from one to**

three decades.

Q Let's turn to PX 1026.

And this is an article that's been admitted, that Dr. Heinecke discussed at his -- during his testimony, and the parties have stipulated that it's prior art to the asserted patents.

THE COURT: And I just realized that it would be helpful to have the paragraph number in the stipulation if you have it because I remember my comment at the start of the trial as to the number of paragraphs.

I did find the stipulation relating to ATP III and that's paragraph 47. So for this article, what paragraph of the stipulation. Do you have that number?

MR. ELIKAN: Paragraph 95.

THE COURT: Thank you.

BY MR. ELIKAN:

Q Looking at the top of the first page, what's -- what was the date of publication?

A This was published in *Atherosclerosis* in 1977.

Q And what triglyceride lowering drug, if any is -- was the subject of this paper?

A Niacin.

Q And I want to look at the summary on the first page. And in the first sentence there's reference to Type V hyperlipoproteinemia? Did I pronounce that right?

09:14:05 A **Yes, you did great, counsel.**

09:14:06 Q **Okay. And you recall that Dr. Heinecke testified that Type V -- can we call it HLP?**

09:14:08 A **Yeah.**

09:14:12 Q **That Type V HLP is very high triglycerides. Do you recall that testimony?**

09:14:12 A **I do.**

09:14:17 Q **Do you agree with him?**

09:14:18 A **I do agree with him.**

09:14:19 Q **Turning back to Carlson, the next sentence makes reference to nicotinic acid. What's nicotinic acid?**

09:14:21 A **It's the same as niacin.**

09:14:22 Q **And what does this sentence say about the effect of nicotinic acid or niacin on LDL in Type V HLP?**

09:14:25 A **That it increases LDL.**

09:14:30 Q **I want to turn to page 3 now, to the second paragraph under Results.**

09:14:32 **What did the authors observe about the effect of nicotinic acid or niacin on LDL cholesterol in patients with Type V HLP?**

09:14:42 A **Well, I quote,**

09:14:46 **"That the rise in LDL and HDL cholesterol is a general phenomenon when Type V HLP is treated is apparent from the results of nine patients with Type V HLP who were treated with diet alone or with**

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nicotinic acid. All four patients treated with diet and all five treated with nicotinic acid had pronounced increases in LDL cholesterol when VLDL fell towards normal values and all about two had increases in HDL cholesterol."

Q And what in plain English does this mean?

A That means that as the VLDL decreased with the niacin therapy, the LDL shot up.

MR. ELIKAN: Let's turn to the last page, page 7. Can we pull up the second paragraph and highlight the first sentence of the paragraph.

BY MR. ELIKAN:

Q What do the authors conclude by the clinical implications of where we saw what Carlson called the general phenomenon that LDL-C increases were observed?

A Well, just a quick reminder it's LDL the cholesterol that's the bad cholesterol. The finding of major clinical concern in this report is the sometimes quite substantial rise in LDL cholesterol.

Q There's italicized major clinical concern there.

A Yes.

Q Is that something that's of considerable importance in practicing medicine and of import to the readers?

A Yes, because if the LDL shoots up, this would heighten risk for the development of the cardiovascular disease.

09:16:56 **MR. ELIKAN: Can we highlight the next sentence now.**

09:16:58 **BY MR. ELIKAN:**

09:17:00 **Q What do the authors explain as the reason why an LDL increase would be -- or would have been a major clinical concern?**

09:17:05 **A They note that this may be quite atherogenic which just means it potentiates the development of heart disease and theoretically the benefit of lowering VLDL in these patients may be overridden by the potential danger due to the rise in LDL.**

09:17:10 **Q Before March of 2008, did subsequent experience with fibrates further inform the perception that large increases in LDL-C were a general phenomenon when lowering triglycerides in patients with very high triglycerides?**

09:17:30 **A Yes, counsel.**

09:17:47 **Q And very generally, what were or what are fibrates?**

09:17:48 **A The fibrates are what we call fibric, f-i-b-r-i-c, acid derivatives. They are molecules that exert effects on lipid and lipoprotein metabolism and they help to reduce VLDL and triglycerides and modestly increase the good or HDL cholesterol.**

09:17:52 **Q As of March 2008 had fibrates been widely used as a lipid altering drug including for severe hypertriglyceridemia?**

09:18:17 **A Yes.**

09:18:25 Q **And what did the experience with fibrates teach about**
09:18:33 **what happened to LDL-C when triglycerides were lowered in**
09:18:38 **patients with very high triglycerides?**
09:18:41 A **The LDL increased in proportion to the baseline**
09:18:44 **triglyceride levels.**
09:18:45 Q **Let's turn to PX 388.**
09:18:55 **Let me ask a question before we look there. This**
09:18:59 **rise, was it observed in patients with very high triglycerides**
09:19:03 **even when the drug didn't rise to a -- or rise or rise**
09:19:09 **dramatically in patients with lower triglycerides?**
09:19:12 A **Counsel, could you pleads repeat that.**
09:19:14 Q **Sure. We were talking about the rise in LDL-C.**
09:19:20 A **Yes.**
09:19:21 Q **So in the very high triglyceride population, you talked**
09:19:28 **about a rise. Was there a large rise in the very high**
09:19:35 **triglyceride population even when the drug didn't do that in**
09:19:39 **patients with lower triglycerides?**
09:19:41 A **Yes, that's correct.**
09:19:44 Q **Now, let's turn to PX 388, this is the Tricor label**
09:19:51 **previously admitted and discussed during Dr. Heinecke's**
09:19:56 **testimony, is that right?**
09:19:57 A **Yes.**
09:19:57 **MR. ELIKAN: And the parties, Your Honor, have**
09:19:59 **stipulated that PX 388 is prior art and that's in paragraph**
09:20:05 **105 of the joint stipulations.**

09:20:07 **THE COURT: Thank you.**

09:20:07 **BY MR. ELIKAN:**

09:20:07 Q **Do you recognize this as the product label for the fenofibrates Tricor?**

09:20:16

09:20:17 A **I do.**

09:20:18 **MR. ELIKAN: Can we turn to Table 1 on page 6 and highlight the title.**

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09:20:22 **BY MR. ELIKAN:**

09:20:24 Q **In general terms what information it contained in this table?**

09:20:27

09:20:27 A **It contains mean percent changes in lipid and lipoprotein parameters at the end of treatment with Tricor.**

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09:20:38 Q **I want to look at the bottom row of the table. Do you see this table describes lipid effects for a group having triglycerides of at least 150?**

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09:20:48 A **Yes.**

09:20:48 Q **And LDL-C exceeding 160?**

09:20:57 A **Yes.**

09:20:57 Q **Looking at the far right of the bottom row, what does the table indicate was the mean baseline triglyceride value of this group?**

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09:21:06 A **It was 231.9 milligrams per deciliter.**

09:21:10 Q **And does the table provide information about the effect of Tricor on LDL-C in those patients?**

09:21:13

09:21:18 A **It does.**

MR. ELIKAN: Now, I want to turn to page 7, Table 2. And can we highlight the title again.

BY MR. ELIKAN:

Q **What information is in this table?**

A **This is a summary of the effects of Tricor in patients with Frederickson Type IV and Type V hyperlipidemia.**

So consistent with what has previously been noted here at trial, the Type V hyperlipidemia would be patients with severe hypertriglyceridemia, and the Type IVs typically have not as severe. They were typically, typically under 500.

Q **Let's look at the table itself. In the top half of the table do you see a reference to Study 1?**

A **Yes.**

Q **And looking at the left-hand column under Study 1, what's the range of triglycerides of patients in Study 1?**

A **350 to 499.**

Q **And looking at the row labeled triglycerides, what does the table indicate was the mean baseline triglyceride level of the patients in the treatment arm in Study 1?**

A **432.**

Q **Does this table provide information about the effect of fenofibrates on the LDL-C levels in this patient population?**

A **Yes, counsel.**

Q **In the bottom half the paper there's reference to Study 2, do you see that?**

09:22:46 A **I do.**

09:22:47 Q **And looking to the left, directly under Study 2, what's the range of baseline triglycerides of patients in Study 2?**

09:22:51 A **500 to 1500.**

09:22:55 Q **So are those patients with very high triglycerides?**

09:22:57 A **Yes.**

09:23:00 Q **Did this table provide information about the effect of fenofibrate on the LDL-C in patients with very high triglycerides?**

09:23:04 A **It did.**

09:23:08 Q **Have you prepared a demonstrative summarizing the information of the Tricor label showing the effects of fenofibrate on LDL-C in these different patient populations?**

09:23:09 A **Yes.**

09:23:10 **MR. ELIKAN: Can we have PDX 6-7.**

09:23:13 **BY MR. ELIKAN:**

09:23:17 Q **What does this illustrate?**

09:23:21 A **Well, moving from left to right, the patients with mixed dyslipidemia with triglycerides greater than or equal to 150 but a mean of 231.9, we see that there is a 20.1 percent reduction in LDL cholesterol compared to baseline.**

09:23:22 Q **A reduction.**

09:23:26 A **Yes. And moving to the middle histogram, the orange one, these were the patients were high triglycerides, 350 to 499, with a mean of 432. And there's a nonsignificant 14**

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09:24:04 and-a-half percent rise in the LDL compared to baseline or
09:24:09 two-and-a-half percent compared to placebo.
09:24:13 And moving all the way to the right, this purple
09:24:17 histogram for the patients with very high triglyceride,
09:24:23 triglycerides 500 to 1500 with mean of 726, the LDL
09:24:29 cholesterol increased 45 percent compared to baseline,
09:24:33 49 percent compared to placebo.
09:24:36 Q And putting this all together, does this mean that
09:24:40 fenofibrate lowered LDL-C in patients with moderately elevated
09:24:46 triglycerides? Is that right?
09:24:48 A Yes.
09:24:48 Q And did not cause a statistically significant rise in
09:24:52 LDL-C with patients with high triglyceride, the 350 to 499.
09:24:58 A That's correct.
09:24:59 Q But caused large statistically significant increases in
09:25:07 LDL-C in patients with very high triglycerides.
09:25:08 A That is also correct.
09:25:11 MR. ELIKAN: Your Honor, we move PDX 6-7 as a
09:25:13 summary under rule 1006, if this would help, Your Honor. It
09:25:17 is in the documents we looked at, and it's a compilation of
09:25:22 that data.
09:25:22 THE COURT: Mr. Klein?
09:25:23 MR. KLEIN: I don't object.
09:25:24 THE COURT: That request is admitted, PDX 6-7
09:25:28 will be admitted as summary exhibit.

(Plaintiffs' Exhibit 6-7 received in evidence.)

THE COURT: And this is part of -- I don't know that I have designated -- well, I just need a way to keep track of demonstrative evidence offered that I admitted as a summary exhibit and I think reference to PDX 6-7 will suffice. Thank you.

BY MR. ELIKAN:

Q What if anything would these LDL-C effects have told a person of ordinary skill in the art in March 2008 about whether LDL-C effects observed in patients with less than 500 would be predictive, absolutely predictive of LDL-C effects in patients with very high triglycerides?

A Well, that would be an incorrect conclusion to draw because clearly in the patients with more moderate hypertriglyceridemia with a mean of 232 actually LDL decreased.

350 to 500 there's no statistically significant rise though there slight right, there's directional increase. But then when you go above 500 you zoom up.

Q Was there other prior art that reported that fibrates had different effects on LDL-C depending upon the patient's baseline triglyceride levels?

A Yes.

MR. ELIKAN: Let's turn to PX 1027.

And, Your Honor, this is the 2006 chapter by

Dr. Mahley in Goodman & Gilman's that Dr. Heinecke testified about. It's pre-admitted, and in the joint stipulations of fact the parties agreed that it was prior art in the asserted patents, and the citation of that is 96.

THE COURT: Eighty-six?

MR. ELIKAN: Ninety-six.

THE COURT: Ninety-six, thank you.

BY MR. ELIKAN:

Q **What is Goodman & Gilman?**

A **Goodman & Gilman is a widely recognized textbook on pharmacology.**

Q **I want to turn to page 6.**

What is this chapter in Goodman & Gilman directed to?

A **The drug therapy for hypercholesterolemia and dyslipidemia.**

MR. ELIKAN: I now want to turn to page 31, and I want to direct your attention to the left-hand column and looking at the second full paragraph, let's highlight the sentence starting with "The second generation agents."

BY MR. ELIKAN:

Q **What does this sentence say about the LDL-C effects of second generation fibrates on LDL-C levels in patients depending on baseline triglyceride levels?**

A **I quote,**

"The second generation agents, such as fenofibrate, bezafibrate, and ciprofibrate, lower VLDL levels to a degree similar to that produced by gemfibrozil, but they also are more likely to decrease LDL levels by 15 to 20 percent. In patients with more marked hypertriglyceridemia, for example, 400 to 1000, a similar fall in triglycerides occurs, but LDL increases of 10 to 30 percent are seen frequently."

Q **What, generally, does this reference tell us about whether the effects of a triglyceride lowering agent on LDL-C in patients with lower baseline triglycerides would be predictive of the LDL-C effects of a triglyceride lowering patients in patients with very high triglycerides?**

A **Well, it instructs us that it's two very different clinical scenarios, because in patients with more mild hypertriglyceridemia, the LDL decreases 15 to 20 percent, but in patients with triglycerides that are more markedly elevated, 400 to a thousand, there's the opposite effect where the LDL increases.**

Q **And is this phenomenon with fibrates, is this a similar or the same phenomenon or a different one as we saw with niacin in the Carlson paper?**

A **It is similar.**

Q **You also mentioned Lovaza when you were listing the**

09:30:27 **approved triglyceride lowering agents approved for very high**
09:30:33 **triglycerides as of March 2008. I want to turn to that now.**
09:30:36 A **Yes.**
09:30:36 Q **Did Lovaza show differential effects on LDL-C depending**
09:30:41 **on the baseline triglyceride levels of the patients?**
09:30:44 A **Yes, counsel.**
09:30:45 **MR. ELIKAN: Let's turn to PX 939.**
09:30:52 **This is the Lovaza statistical review which has**
09:30:55 **been pre-admitted, Your Honor, and the parties have stipulated**
09:30:59 **that it's prior art in paragraph 87?**
09:31:04 **THE COURT: Thank you.**
09:31:04 **BY MR. ELIKAN:**
09:31:06 Q **Do you understand this to be the statistical review that**
09:31:09 **was generated in conjunction with the development of Lovaza?**
09:31:12 A **I do, counsel.**
09:31:13 Q **I want to turn to page 5 and the first paragraph under**
09:31:19 **executive summary.**
09:31:20 **Do you see a reference to K85?**
09:31:28 A **Yes.**
09:31:28 Q **What is that?**
09:31:29 A **K85 is the something developmental designation for**
09:31:29 **Lovaza.**
09:31:33 Q **Is that the same thing as Omacor?**
09:31:33 A **Yes.**
09:31:36 **MR. ELIKAN: I want to look now at the next**

paragraph in executive summary and can we highlight the first two sentences.

BY MR. ELIKAN:

Q What does the statistical review state were the category 1 studies that were conducted as part of the review?

A It says,

"The efficacy of the 4-gram per day K85 is based on eight double-blind, placebo-controlled, randomized, parallel group studies or parts of study that used K85 4-milligram dose per day. These Category 1 studies included a eight week dose response study, five European studies that had dietary run-in phase, 9 or 10 weeks, and a 12-week double-blind treatment phase, and two U.S. studies in patients with severe hypertriglyceridemia,"

which they defined as triglycerides greater than or equal to 500.

Q So that's five European studies and two U.S. studies?

A Yes, counsel.

MR. ELIKAN: Now, I want to turn to page 6, Table 2. Can we highlight the entries for baseline triglycerides for the treatment arms in the European and US studies, Mr. Brooks.

BY MR. ELIKAN:

Q What were the baseline triglyceride levels for these two

groups?

A For the European group it was 275 milligrams per deciliter, and for the United States group it was 816.

Q So was the US population a population of severely hypertriglyceridemic patients?

A Yes.

Q Does the table report the percent change in both triglycerides and LDL-C for these groups?

A Yes.

Q Have you prepared a slide that shows what these Lovaza studies revealed about the different LDL-C effects of Lovaza in patients with very high triglyceride, compared to the patients with lower triglycerides?

A Yes, counsel.

MR. ELIKAN: Can we have PDX 6-8.

BY MR. ELIKAN:

Q And what does this illustrate about the effects of Lovaza on LDL-C in these two groups?

A If we begin with the left-hand blue histogram, this represented the high triglyceride group with median of 275.

Q So is that the European group?

A Yes. And what we find is that the LDL cholesterol increased four-and-a-half percent compared to baseline or 6.9 percent compared to placebo.

And as we move to the right looking at the orange

histogram, these were the patients in the United States with very high triglycerides median of 816 milligrams per deciliter.

You see there is a ten-fold higher increase in the LDL-C compared to baseline at 44.15 percent or 49.3 percent compared to placebo.

Q **And what if anything does this show about the relationship between LDL-C and patient baseline triglyceride levels?**

A **That the two groups are very different in terms of how they behave, with their LDL responses.**

Q **And in view of the earlier -- the experience with the earlier approved triglyceride lowering agents, including fibrates, to what would a person of ordinary skill in the art have attributed the large rise on the right observed with Lovaza as administered to patients with very high triglycerides?**

A **As an increase in conversion of VLDL to LDL.**

Q **And to what would they have attributed that?**

You said VLDL to LDL, is that the metabolic pathway that you described before?

A **Yes.**

Q **Would they have see that as part of the -- that's specific to the drug that's administered, or is it more generally part of the general way in which triglycerides are**

lowered?

A Well, because we see it with the niacin, the fibrates as well as the Lovaza, it would have been seen as part of the general means by which triglycerides and VLDLs are reduced when using a drug.

Q So the metabolic pathway that we discussed, is that the same thing as -- you also used the term of backlog I think or a logjam.

MR. ELIKAN: Your Honor --

THE WITNESS: Breaking the logjam.

BY MR. ELIKAN:

Q Is that breaking the logjam phenomenon something that's discussed in the literature existing in March 2008?

A Yes, widely discussed.

MR. ELIKAN: I want to go to PX 923. This is the McKenney and Sica reference from 2007. It's been pre-admitted, and, Your Honor, the parties have stipulated that it's prior art in paragraph 85.

THE COURT: Thank you.

MR. ELIKAN: Can we go to page 3? We're there already.

BY MR. ELIKAN:

Q Looking at the title what's the general subject matter of this paper?

A It's the prescription of omega-3 fatty acids for the

treatment of hypertriglyceridemia.

MR. ELIKAN: Can we pull up page 5, and I want to highlight the first sentence of the paragraph that starts at the lower left-hand column.

BY MR. ELIKAN:

Q **What does McKenney have to say here in the first sentence of this paragraph?**

A **Dr. Kennedy notes,**

"The triglyceride reducing effects of EPA and DHA have been detailed in numerous studies among a wide range of patient types."

Q **And looking a little further down this paragraph, but in the middle column of the same page, I want to highlight the first full sentence six lines down starting with "as with fibric acid derivatives."**

What does Dr. McKenney state here about omega-3 fatty acids and how they compare to the earlier -- the other -- the drugs that you discussed earlier the fibric acid derivatives and nicotinic acid.

A **He notes,**

"As with fibric acid derivatives (fibrates) and nicotinic acid (niacin), reductions in triglycerides and very low density lipoprotein or VLDL are generally greater in patients with higher baseline triglyceride levels."

09:38:20 Q **Can we continue on to the next sentence. What does he report there?**

09:38:23 A **I quote,**

09:38:24 **"An increase in LDL and HDL cholesterol can accompany a reduction in triglycerides. The higher the baseline triglyceride level, the greater these lipids may be increased."**

09:38:26 09:38:31 09:38:34 09:38:36

09:38:39 Q **So is this the same phenomenon that you've been discussing now and that you've observed in numerous places we've looked through?**

09:38:43 09:38:46

09:38:47 A **Yes.**

09:38:48 Q **And in a nutshell, how does Dr. McKenney understand omega-3 fatty acids to perform with regard to LDL-C levels, like fibrates and niacin or differently?**

09:38:48 09:38:59

09:38:59 A **Like fibrates and niacin.**

09:39:03 **MR. ELIKAN: Now, I want to look at the last paragraph in the right-hand column of page 5. Can we highlight the first sentence, Mr. Brooks.**

09:39:05 09:39:09

09:39:09 **BY MR. ELIKAN:**

09:39:15 Q **What does this sentence indicate the paragraph is generally about?**

09:39:17

09:39:19 A **He's going to discuss the pharmacokinetics of lipoproteins in response to omega-3 fatty acids.**

09:39:25

09:39:27 Q **Okay. And I want to look down to the middle of paragraph to the fourth sentence starting with "importantly." What does**

09:39:30

09:39:33 **Dr. McKenney report about the reports about the**
09:39:39 **pharmacokinetic study on omega-3 fatty acids?**
09:39:40 **A That the conversion of VLDL to LDL particles increased 93**
09:39:52 **percent under the influence of the omega-3 fatty acids.**
09:39:52 **Q What does that mean in nutshell as far as your logjam**
09:39:56 **analogy?**
09:39:56 **A That means that the omega-3s break the logjam and**
09:39:56 **increase the conversion of the VLDL to the LDL.**
09:40:02 **Q I want to highlight the rest of the paragraph now.**
09:40:05 **And as you what conclusion does Dr. McKenney draw**
09:40:12 **about the consequence of this increased conversion of VLDL to**
09:40:18 **LDL as far as LDL-C levels are concerned?**
09:40:22 **A He notes that,**
09:40:23 **"These results illustrate that the enhanced**
09:40:26 **catabolism of triglycerides produced by the omega-3**
09:40:28 **fatty acids results in less secretion and more rapid**
09:40:32 **removal of VLDL particles. The results also show**
09:40:37 **that VLDL particles are rapidly converted to LDL**
09:40:42 **particles, thus explaining why LDL cholesterol levels**
09:40:47 **may rise in patients with very high triglycerides**
09:40:49 **when given omega-3 fatty acid therapy."**
09:40:52 **Q And can you explain what that is -- what he's saying**
09:40:55 **there in less technical language.**
09:40:57 **A Sure. He is saying that the omega-3 fatty acids decrease**
09:41:03 **the secretion of VLDL particles, facilitate their removal from**

serum, but also that for VLDLs in serum the omega-3 fatty acids increase their rate of conversion to LDL, which is why the LDL zooms up.

Q In your work on this case, did you review other literature existing as of March 2008 that showed that omega-3s increased the conversion rate of VLDLs to LDL?

A Yes.

MR. ELIKAN: Can we have PX 562.

And this, Your Honor, has been pre-admitted. It's a 2006 article by Dr. Balk, and the parties have stipulated that it is prior art and that's in paragraph 73.

THE COURT: Thank you.

BY MR. ELIKAN:

Q What does this reference concern?

A This is a paper published in *Atherosclerosis* in 2006 and it's review article.

It evaluates the effects of omega-3 fatty acids on serum markers of cardiovascular disease risk.

Q I want to turn to page 9, in the upper left-hand corner. What does the final sentence of this paragraph, the one beginning with "additionally," what does it state about the mechanism of omega-3 fatty acids?

A It states,

"Additionally, there is some evidence that omega-3 fatty acids increase the conversion rate of

VLDL to LDL, similar to fibrate drugs."

Q And is Balk in his review article saying the same or something different from what we just saw in Dr. McKenney's paper?

A The same.

Q And did you consider other prior art attributing the increase in LDL-C seen in patients with very high triglycerides as something that results from the conversion of VLDL to LDL?

A Yes, counsel.

MR. ELIKAN: Can we have PX 486, please.

This is a Bays 2008 article, Dr. Bays is the author, Prescription Omega-3 Fatty Acids, it's been pre-admitted and the parties stipulated that it's prior art that's in paragraph 69.

BY MR. ELIKAN:

Q Dr. Toth very briefly what does this publication concern?

A This publication looks at the impact of the omega-3 fatty acids on lipid effects with emphasis on physiologic mechanisms of action.

MR. ELIKAN: Let's go to page 10 and I want to highlight the second to last sentence on page ten as well as the next two sentence which carry over to page 12.

BY MR. ELIKAN:

Q In these two sentences, what does Dr. Bays report about

09:44:10 **the effect of fibrates in omega-3 fatty acids on LDL-C?**

09:44:17 **A "As with fibrates, the degree of LDL-C**

09:44:21 **elevations observed with omega-3 treatment is**

09:44:25 **generally related to the pretreatment triglyceride**

09:44:27 **levels. Omega-3 fatty acids increase LDL cholesterol**

09:44:32 **levels the most in patients with the highest**

09:44:36 **pretreatment triglyceride levels. The reason for the**

09:44:38 **increased LDL cholesterol levels with omega-3 fatty**

09:44:44 **acids is related to the increased conversion of VLDL**

09:44:48 **particles to LDL particles."**

09:44:51 **Q Is this the same or a different phenomenon from what we**

09:44:55 **saw in Dr. McKenney's paper and Dr. Balk's paper?**

09:45:00 **A It's the same counsel.**

09:45:01 **Q Do you recall that Dr. Heinecke testified that some prior**

09:45:05 **art references showed that triglyceride-lowering agents**

09:45:08 **administered to patients who have elevated triglycerides, did**

09:45:11 **not have substantial increases in their LDL-C levels. Do you**

09:45:18 **recall that testimony?**

09:45:19 **A Say that again, counsel.**

09:45:20 **Q Do you recall that Dr. Heinecke testified that some prior**

09:45:24 **art references showed that triglyceride-lowering agents**

09:45:28 **administered to patients who have elevated triglycerides did**

09:45:33 **not have substantial increases in their LDL-C levels?**

09:45:40 **A Yes.**

09:45:40 **Q Okay. Now, I want to focus not merely on elevated**

triglycerides but on severe hypertriglyceridemia.

Would a person of ordinary skill in the art in March 2008 have viewed the LDL-C effects of those agents in patients with triglyceride levels below 500, as informative about the LDL-C effects expected in patients with triglyceride levels of at least 500?

A **No.**

Q **And why not?**

A **Well, we just reviewed some of the evidence here with Lovaza, with niacin, with fenofibrate or fibrates, and the populations below and above 500 clearly behave very differently when it comes to the expected or observed change in LDL cholesterol.**

Q **In putting this all together as of March 2008, did any agents, any approved for severe hypertriglyceridemia, avoid these increases in LDL-C?**

A **They did not.**

Q **Do you recall that Dr. Heinecke testified that the LDL-C increases with Lovaza and other triglyceride lowering agents could be addressed by adding a statin which had been shown to decrease LDL-C?**

A **Yes.**

Q **Is it always possible to add a statin?**

A **Well, it's not always possible to add a statin because some patients are simply statin intolerant. This is**

well-established in the literature.

But even in some situations where you can add a statin, there may be those limitations as to what a patient can tolerate because of side effects.

And the other concern here is, and believe me, we do what we have to do, sure, we can add statins, but one of the biggest concerns with patients with severe hypertriglyceridemia is we saw that with Lovaza, with fibrates, these increases in LDL can approach 50 percent, but that's the average. It can be significantly higher than that if you look at the distribution of the values.

Currently available high dose high potency statins can reduce LDL about 55 percent. So if a patient did tolerate a high dose high potency statin and their LDL went up 50, 55 percent, you just burned all your statin lowering capacity just to get them back to baseline.

So it's not always possible for these different reasons, but we do the best we can.

Q **Now, we've been discussing the -- triglyceride lowering agents that were approved as of 2008 substantially raised LDL-C in patients with very high triglycerides.**

Beyond that drawback, did these approved triglyceride lowering agents have other draw backs?

A **Yes, side effects.**

Q **Let's talk about niacin. So other than the LDL-C**

increase, what drawbacks did niacin have?

A **Well, niacin was challenging to use because niacin could induce head to toe flushing, which is where the small blood vessels in the skin dilate and the patient actually looks red because their skin is so engorged with blood from this flushing.**

This can result in a very intense sensation of heat, itching, tingling. And for anyone who has experienced that at 2 in the morning, you might not want to do it again.

And niacin also was shown subsequently to increase risk for some types of infection. So, yes, there were drawbacks.

Q **Would you say that niacin had a good side effect profile or not so good?**

A **Not so good. And not that many, not a very high percentage of patients could tolerate it.**

Q **Is that something you observed in your own practice?**

A **Yes.**

Q **And was that reflected in the prior art?**

A **Yes.**

Q **Let's go to PX 883.**

And do you recognize PX 883?

A **Yes, counsel.**

Q **What is it?**

A **It's Goodman & Gilman's, *The Pharmacological Basis of***

09:50:28 ***Therapeutics***.

09:50:29 Q **And if we look at the copyright date on page 2 --**

09:50:34 A **It's --**

09:50:35 Q **When was it published?**

09:50:36 A **1980.**

09:50:38 Q **Could we look at the next page. And what is this chapter?**

09:50:47 A **It's a chapter by Bob Levy on drugs used in the treatment of hyperlipoproteinemias.**

09:50:55 Q **We saw before a copyright date 1980, was this then publically available as of March 2008?**

09:51:02 A **Most certainly.**

09:51:07 **MR. ELIKAN: We move to move PX 883 into evidence.**

09:51:10 **MR. KLEIN: No objection.**

09:51:11 **THE COURT: PX 883 is admitted.**

09:51:11 **(Plaintiffs' Exhibit 883 received in evidence.)**

09:51:15 **MR. ELIKAN: Thank you, Your Honor.**

09:51:16 **Can we turn to page 8, the right-hand column under untoward effects. Can we highlight the first three sentences.**

09:51:20 **BY MR. ELIKAN:**

09:51:29 Q **What does?**

09:51:30 A **He states,**

09:51:31 **"There are several untoward effects of**

09:51:34 **nicotinic acid that limit its usefulness. Notably,**
09:51:39 **the drug produces intense cutaneous flush and**
09:51:44 **pruritus. While these reactions" --**
09:51:45 Q **Hold on one second. What's pruritus?**
09:51:48 A **Pruritus is itching of the skin.**
09:51:51 Q **Okay. I'm sorry.**
09:51:53 A **I'll spell it for the court reporter, p-r-u-r-i-t-i-s.**
09:51:57 **And I'll continue, counsel.**
09:51:57 **MR. ELIKAN: Thank you.**
09:52:00 **THE WITNESS: "While these reactions**
09:52:01 **decrease in intensity in most individuals after**
09:52:05 **they have been on therapy for several weeks, they**
09:52:07 **are unpleasant and result in poor patient**
09:52:11 **compliance."**
09:52:11 **BY MR. ELIKAN:**
09:52:11 Q **The author of this chapter Dr. Levy, who is or was he?**
09:52:20 A **He was a very prominent lipidologist at the National**
09:52:24 **Institutes of Health and he's also the same Dr. Levy of the**
09:52:29 **Levy-Fredrickson dyslipidemia classification.**
09:52:32 Q **And it would include the Type V HLP that we looked at**
09:52:38 **earlier?**
09:52:38 A **Yes.**
09:52:38 Q **I want to ask you about some of the other limitations. I**
09:52:42 **want to ask you now about limitations of fibrates.**
09:52:45 **In addition to LDL-C increases in patients with very**

high triglycerides, did fibrates have other drawbacks?

A Sure.

Q What were they?

A Well, the fibrates, if you take the example of gemfibrozil which was widely available prior to the priority date, its biggest drawback was that it strongly interacted with the statins. And by strongly interacted I mean it could inhibit statin metabolism which could lead to a precipitous rise in serum statin levels which could then precipitate the most dreaded complication of statin therapy which is rhabdomyolysis or what Dr. Fisher called Rhabdo.

And this is a diffuse dissolution of skeletal muscle cells that could also result in acute renal failure. So this was truly a medical emergency.

But there were others, there could be elevation in liver enzymes, there could be muscle aching. There were multiple side effects?

MR. ELIKAN: I want to look back at PX 923, the McKenney article. Could we have page 10 on the screen. And I want to highlight the second sentence in the first full paragraph in the middle column.

BY MR. ELIKAN:

Q What does Dr. McKenney say here about fibrates?

A Fibrates can cause myopathy or injury to muscle and rhabdomyolysis, and court reporter -- let me spell that.

R-h-a-b-d-o-m-y-o-l-y-s-i-s. And should be used in caution with individuals at a high risk of these problems.

Q **He says fibrates in the plural. Is he limiting his observation to gemfibrozil?**

A **No, counsel.**

Q **I want to turn now to Vascepa. Has Vascepa addressed the limitations of these earlier products?**

A **Yes.**

Q **How?**

A **Vascepa was the first pharmacologic intervention in the setting of severe hypertriglyceridemia which provided the clinical meaningful reductions in triglycerides without increasing LDL cholesterol, and it had a very favorable side effect profile.**

Q **Can it be administered a statin?**

A **Yes.**

Q **None of the safety concerns that you spoke of moment ago.**

A **No.**

Q **I want to turn now to clinical trials involving Vascepa starting with MARINE.**

MR. ELIKAN: Can we turn to PX 807, the clinical study report of MARINE.

And this was pre-admitted and the subject of testimony by Dr. Ketchum, Your Honor.

THE COURT: Is this the MARINE study?

MR. ELIKAN: Yes.

THE COURT: Thank you.

MR. ELIKAN: It's indicated in last line of the title.

BY MR. ELIKAN:

Q Turning to page 11 there's section titled Conclusions. What does the first sentence say about the triglyceride levels of the population studied?

A "In a population of patients with very high triglycerides," which would be greater than 500 --

Q So that's the population that was studied, Doctor?

A Yes sir.

Q Okay. I want to highlight the last sentence of the first paragraph of this section beginning with "in contrast."

A Yes.

Q What did the MARINE trial report about the effects of Vascepa on LDL-C?

A "In contrast to other triglyceride lowering agents, the reduction in triglyceride levels was not associated with an elevation in LDL cholesterol levels compared to placebo."

MR. ELIKAN: Now, I want to go to page 111, and can we pull up table 29, Mr. Brooks, and highlight the title.

BY MR. ELIKAN:

Q And what does table 29 generally concern?

09:56:47 A **This is a Summary of the Treatment Emergent Adverse**
09:56:52 **Effects of Interest By System Organ Class and Preferred Term**
09:56:56 **During the Double-Blind Treatment Period - Safety Population.**
09:57:00 Q **Do you see a column for AMR 101, 4 grams?**
09:57:04 A **Yes.**
09:57:05 Q **Do you recall what that refers to?**
09:57:07 A **Yes, AMR 101 would be the developmental designation for**
09:57:12 **Vascepa.**
09:57:13 Q **And in general, we don't need to go into the specific,**
09:57:17 **but in general what do the authors report here? What does the**
09:57:21 **study report show about how Vascepa, at four grams compared to**
09:57:25 **placebo in terms of adverse events?**
09:57:28 A **Very favorably. In fact, for multiple side effects,**
09:57:34 **numerically Vascepa had a lower rate for some sigh effects**
09:57:38 **than did placebo.**
09:57:39 Q **And following publication of the MARINE results, did you**
09:57:43 **begin to prescribe Vascepa for patients with very high**
09:57:48 **triglycerides?**
09:57:48 A **Yes.**
09:57:49 Q **Following announcements, announcement of the results of**
09:57:54 **the MARINE trial, have other clinicians recognized Vascepa as**
09:58:00 **an advance in the treatment of severe hypertriglyceridemia?**
09:58:03 A **Yes, counsel.**
09:58:04 Q **Let's turn to DX 1581. This is the O'Riordan article**
09:58:11 **previously admitted that Dr. Heinecke discussed. And I want**

09:58:15 to turn to the second paragraph on page 1?

09:58:19 And what does that first sentence state had been

09:58:24 reported that very day.

09:58:25 A That top line results of the MARINE trial, a randomized

09:58:30 placebo-controlled trial testing ethyl EPA in 229 patients

09:58:36 with triglyceride levels greater then or equal to

09:58:39 500 milligrams per deciliter were announced by the Amarin

09:58:42 corporation.

09:58:43 Q So it was the top line results announced that day?

09:58:46 A Yes.

09:58:46 Q And what are top line results?

09:58:49 A Top line results would be the primary endpoint of the

09:58:51 study.

09:58:52 Q Does this mean that a full study report had been

09:58:56 published or is this something preliminary?

09:58:58 A No it's customary to only announce the top line results

09:59:02 prior to publication in a peer review journal where the more

09:59:06 comprehensive report would be provided.

09:59:08 Q And in the next sentence of this paragraph, what had been

09:59:12 reported as far as the top line results are concerned?

09:59:16 A That the 2 and 4-gram doses of Vascepa as the ethyl EPA

09:59:23 is currently known -- well, it was AMR 101 at the time,

09:59:27 reduced triglyceride levels 20 and 33 percent respectively all

09:59:32 without a significant increase in LDL cholesterol levels.

09:59:36 Q I want to direct your attention to the paragraph

immediately above that headed MARINE trial to quote from a person named McGuire. Do we have that on the screen?

A **Yes.**

Q **Who is McGuire?**

A **Dr. Daren McGuire is a prominent cardiologist at VT Southwestern in Dallas.**

Q **And that's indicated in the paragraph immediately above?**

A **Yes.**

Q **In the paragraph that we were looking at right above the heading MARINE trial, what did Dr. McGuire have to say in this statement?**

MR. KLEIN: Objection, Your Honor. I'll object on hearsay. To the extent they're not offering it for the truth of the matter asserted therein, I'm okay. But it's obviously hearsay.

THE COURT: Well, the document is already admitted, isn't it?

MR. KLEIN: The document is admitted, but to the extent he's asking specific questions about the comments, the statements from someone else, I just want to clarify for the record that we object on hearsay grounds to that type of testimony.

THE COURT: Counsel, what's your response?

MR. ELIKAN: Well, Your Honor, I believe Dr. Heinecke discussed statements in this same article and

10:00:54 there was no issue with defendants' put being forward those
10:00:58 statements. The document is already been admitted.
10:01:00 THE COURT: I'm assuming you're just
10:01:03 highlighting the statement.
10:01:04 MR. ELIKAN: Correct.
10:01:05 THE COURT: In other words you're not going to
10:01:06 go into details what the statement means. You're just asking
10:01:08 him to read --
10:01:08 MR. ELIKAN: I'm going to go into detail.
10:01:10 THE COURT: You are or are not?
10:01:12 MR. ELIKAN: Yes, I am but not after offering it
10:01:14 for the truth of the matter asserted.
10:01:16 THE COURT: Then there's no -- that would
10:01:17 resolve any objection.
10:01:18 MR. KLEIN: Yes.
10:01:19 MR. ELIKAN: I think it would.
10:01:20 THE COURT: All right.
10:01:20 BY MR. ELIKAN:
10:01:24 Q So in the paragraph right above the heading MARINE Trial,
10:01:28 what did Dr. McGuire have to say here?
10:01:32 A He notes,
10:01:32 "At the end the day, if you can have
10:01:34 favorable cardiovascular effects without raising LDL
10:01:39 cholesterol, that's going to be an advantage.
10:01:41 There's a lot of enthusiasm for this compound, but

this it really early in development and I would insert a note of caution here the early results are intriguing."

Q And how do you understand this statement the early reports are intriguing?

A Well, the full report hadn't been published yet. He's responding to the top line results which he finds intriguing.

Q And how do you understand his statement about the need for a dose of caution?

A Because he wants to see the full report. He wants to see if there's any side effects. He wants to see exactly what happened to the full range of the lipid profile.

Q And turning to the next page, let's look at the paragraph starting with Dr. Steven Nissen. Do you see that, Doctor?

A I do.

Q Who is Dr. Steven Nissen.

A Steve was the former chief of the cardiology at the Cleveland Clinic in Cleveland Ohio.

Q Now, the last sentence notes that and I quote,

"'The semi synthetic ethyl EPA which does not include DHA in the formulation and has no effect on LDL cholesterol levels is a real advance in the treatment of elevated triglycerides,' he told Heart Wire."

How do you understand his statement that Vascepa

10:03:00 **is a real advance in the treatment of elevated triglycerides?**
10:03:04 **A Because this hadn't been shown before. Steve is a**
10:03:07 **clinical trialist. He knew the landscape and he's just**
10:03:12 **acknowledging excitement over a development where no one had**
10:03:21 **previously found a solution.**
10:03:23 **Q What are you referring to, to the development that nobody**
10:03:26 **had found a solution to?**
10:03:27 **A The Vascepa being able to reduce triglycerides in**
10:03:30 **patients with severe hypertriglyceridemia without raising LDL.**
10:03:34 **Q Now, in the first sentence, Dr. Nissen noted some caveats**
10:03:43 **about trial size and duration of the MARINE trial about which**
10:03:47 **Dr. Heinecke testified as well as the lack of peer review. Do**
10:03:51 **you recall Dr. Heinecke's testimony about this?**
10:03:53 **A Yes.**
10:03:53 **Q I want to look at those caveats now.**
10:03:56 **Did FDA proceed to approve Vascepa for very high**
10:04:01 **triglycerides based on the MARINE trial, irrespective of**
10:04:07 **Dr. Nissen's concerns?**
10:04:08 **A Yes.**
10:04:08 **Q They didn't have an issue with the sample size?**
10:04:10 **A No.**
10:04:11 **Q Or its study design?**
10:04:13 **A No. If they did they wouldn't have approved it.**
10:04:16 **Q And how did the sample size of the MARINE trial compare**
10:04:20 **to the number of subjects that received EPA in the Mori**

reference that Dr. Heinecke discussed in his testimony?
A There are three-and-a-half to four times as many patients per group.
Q And how does the number of subjects in MARINE compare to the number of subjects in Hayashi?
A It's significantly greater.
Q Let's talk about peer review. At the time the article was published, I think we already covered this, but had this been published in a peer review journal?
A Not yet.
Q At a later juncture did the final results, were the final results published in a peer review publication?
A Yes, in the American Journal of Cardiology.
Q Turning to the next paragraph of this article what did Dr. Nissen have to say about Vascepa?
A He notes,

"It gives you all the benefit without the downside. It's an interesting wrinkle, there's still room for small companies to do innovative things in this field."

Q And how do you understand his statement that Vascepa gives you all the benefits without the downside?
A That it dropped the triglycerides without raising the LDL.
Q Since Vascepa entered the market has there been other

10:05:39 recognition among clinicians that Vascepa lowers triglyceride
10:05:43 in patients with very high triglycerides without substantially
10:05:46 raising LDL-C or causing serious side effects?
10:05:50 A Yes counsel.
10:05:51 Q Have you prepared a slide summarizing some of that
10:05:54 recognition?
10:05:54 A Yes.
10:05:55 MR. ELIKAN: Can we have PDX 6-9, please.
10:05:55 BY MR. ELIKAN:
10:05:59 Q And before we talk about the contents, can you identify
10:06:02 the exhibits referenced in the slide.
10:06:05 A Yes, there are two manuscripts the first is by Fialkow,
10:06:12 F-i-a-l-k-o-w, published in 2006 in the American Journal of
10:06:17 Cardiovascular Drugs and this is PX 852.
10:06:21 Q Doctor, you said 2006 or at least that's what I heard.
10:06:24 A 2016.
10:06:27 Q That's PX 582?
10:06:33 A Yes.
10:06:34 Q And on the right?
10:06:36 A One on the right published by Castaldo 2016 in Drugs and
10:06:43 Therapy Perspective, and this PX 866.
10:06:44 Q Did you review each of these articles and rely on them in
10:06:48 forming your opinions?
10:06:49 A Yes.
10:06:49 MR. ELIKAN: We move for admission PX 852 and

866.

MR. KLEIN: No objection.

THE COURT: 852 and 866 are admitted.

(Plaintiffs' Exhibits 852 and 866 received in evidence.)

BY MR. ELIKAN:

Q I want to walk through now what each of these articles say about Vascepa. Can you do that for us starting with Fialkow.

A Yes. Dr. Fialkow notes,

"Use of products containing both DHA and EPA also require periodic monitoring of LDL-C during therapy due to the potential for increases in this lipid parameter while treatment with the EPA only product, icosapent ethyl or Vascepa has no LDL-C monitoring requirement."

Q And Castaldo?

A Dr. Castaldo notes,

"Switching statin add-on therapy from fenofibrates to icosapent ethyl or Vascepa maintained or improved the lipid profile and was well-tolerated with no adverse reactions in a series of patients with hypertension and high cardiovascular risk. Important differences between icosapent ethyl and other add-on therapy options include its good safety and tolerability profile and the fact that it does

10:08:00 not increase LDL-C levels as supported by clinical
10:08:05 studies and the icosapent ethyl or Vascepa product
10:08:08 label."
10:08:08 Q And tying these two articles together, what are the
10:08:13 authors saying here about the effect of Vascepa, if any, on
10:08:17 LDL-C in patients with very high triglycerides?
10:08:20 A It's neutral.
10:08:22 Q And by neutral, do you mean that it doesn't raise LDL-C?
10:08:31 A Yes, and hence, does not require monitoring.
10:08:35 Q Are the statements in these articles, to your view an
10:08:38 accurate reflection of the views of the medical community
10:08:43 about the effects of Vascepa on LDL-C?
10:08:45 A Yes, this was widely acknowledged.
10:08:48 Q Since you began prescribing Vascepa to patients has an
10:08:52 additional clinical trial provided further reasons for you to
10:08:57 prescribe Vascepa to your patients?
10:08:58 A Yes.
10:08:59 Q What trial?
10:09:00 A REDUCE-IT.
10:09:01 MR. ELIKAN: Can we have PX 1189.
10:09:08 And, Your Honor, this was previously admitted
10:09:11 with Dr. Ketchum it's the REDUCE-IT clinical study report.
10:09:13 Let's turn to page 135 and I want to look at the
10:09:17 paragraph at the bottom.
10:09:17

10:09:17 **BY MR. ELIKAN:**

10:09:19 **Q There's reference to Figure 11-3 in that paragraph, do**

10:09:27 **you see that?**

10:09:27 **A I do.**

10:09:29 **Q What does it say about Figure 3?**

10:09:33 **A This is --**

10:09:33 **Q What information does this paragraph say is contained in**

10:09:37 **Figure 11-3?**

10:09:38 **A "A forest plot of the analyses of the**

10:09:41 **individual components of the primary and key**

10:09:41 **secondary endpoints, each analyzed as independent**

10:09:49 **endpoints namely time to first occurrence of nonfatal**

10:09:51 **myocardial," or heart attack, "regardless of the time**

10:09:54 **to first occurrence of any other endpoints for the**

10:09:57 **same patient) is presented."**

10:09:59 **Q So all of that is in Figure 11-3?**

10:10:01 **A Yes.**

10:10:04 **MR. ELIKAN: Let's see how primary and secondary**

10:10:11 **endpoints are defined. Can we turn to page 131 under the**

10:10:15 **heading Primary Endpoint Analysis.**

10:10:15 **BY MR. ELIKAN:**

10:10:18 **Q What does it state about how the primary composit**

10:10:22 **endpoint was defined.**

10:10:26 **A It included five components, cardiovascular death,**

10:10:29 **nonfatal MI including silent MI.**

10:10:32 Q **That's a heart attack, MI?**

10:10:34 A **Yes, sir. EKGs were performed annually for the detection of silent MIs or heart attacks, nonfatal stroke, coronary revascularization would be lack stinting or bypass and unstable angina determined do be caused by myocardial ischemia by invasive-noninvasive testing and requiring emergent hospitalization.**

10:11:00 Q **So all of those together are the primary endpoint?**

10:11:03 A **Yes.**

10:11:03 Q **Now, let's turn to page 134 under 11.4.1.2. What does this indicate -- and we can highlight the first sentence -- about how the key -- the secondary endpoint was defined, the key secondary composit endpoint.**

10:11:23 A **The key secondary composite endpoint was from the time from randomization to the first occurrence of the composite of cardiovascular death, nonfatal MD or heart attack, including silent MI, or nonfatal stroke.**

10:11:43 Q **And with those definitions in mind, let's turn to Figure 11-3 on page 137, the forest plot.**

10:11:54 **Do you understand this graph to be presenting a comparison of the relative risk of cardiovascular events in patients taking Vascepa and a statin as compared to patients who were just taking a placebo and statin?**

10:12:09 A **Yes, counsel.**

10:12:09 Q **Let's run through this table quickly.**

10:12:12 **Looking at this figure, how did Vascepa compare to placebo in terms of the primary composite endpoint?**

10:12:16 A **Well, the primary composite endpoint was reduced by 25 percent. You notice that as we go across the figure, 705 people sustained a component of the primary composite endpoint in the Vascepa group versus 901. And those are the data used to calculate that hazard ratio.**

10:12:36 Q **Is that percentages afterwards?**

10:12:40 A **Yes.**

10:12:42 Q **So --**

10:12:44 A **So the .75 arises from seven --**

10:12:45 Q **Before we get to the .75, what is the percentage that the 705 over 4089 represents and what do we see as the percentage in placebo?**

10:12:50 A **That ratio would constitute the hazard ratio.**

10:12:56 Q **Okay. The 17.2 and the 22 percent together?**

10:12:59 A **Yes.**

10:13:02 Q **Okay. Explain what a hazard ratio is.**

10:13:05 A **A hazard ratio compares the incidence of an endpoint in the treatment arm compared to the placebo group.**

10:13:11 Q **And how is the hazard ratio here related to relative risk reduction?**

10:13:11 A **Well, in general, it would be one minus .75, or 25 percent.**

10:13:15 Q **So is this a 25 percent relative risk reduction?**

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10:13:41 A **Yes, it is statistically highly significant with a P value of .0001.**

10:13:45

10:13:48 Q **And what does this figure report for the relative risk reduction for Vascepa in terms of the key secondary composite endpoint?**

10:13:51

10:13:56

10:13:56 A **It reports a 26 percent relative risk reduction also statistically highly significant.**

10:14:01

10:14:03 Q **What about for cardiovascular death?**

10:14:06 A **20 percent, statistically significant, P equals .03.**

10:14:13 Q **What about for nonfatal myocardial infarction?**

10:14:17 A **That was reduced by 31 percent, P less than .0001.**

10:14:26 Q **Nonfatal stroke.**

10:14:28 A **Nonfatal stroke was reduced by 28 percent, P value .01.**

10:14:36 Q **Doing the math, I came up with 29. You came up with 28.**

10:14:40 A **Yes, sir. I'm sorry, *The New England Journal of Medicine* paper reports 28 and here it reports 29.**

10:14:43

10:14:46 Q **Coronary revascularization, what relative risk reduction is reported?**

10:14:53

10:14:53 A **That is 33 percent, P less than .0001.**

10:14:59 Q **And are all of these statistically significant differences?**

10:15:03

10:15:04 A **They are across the board.**

10:15:05 Q **I want to turn to page 195, Table 11-24. And what in general terms -- we can highlight the title. What in general terms does this table concern?**

10:15:15

10:15:19

10:15:20 A **This looks at stratified analysis of time to the primary endpoint from date of randomization by baseline triglyceride tertiles.**

So what they did was they split the REDUCE-IT cohort into thirds or tertiles to analyze different cut points on the triglycerides.

Q **And what are the triglyceride ranges for each of the tertiles in the table?**

A **81 to less than 190.**

Q **That's for the TG lowest tertile?**

A **Yes, the lowest tertile. The middle tertile was greater than 190 to less than 0 equal to 250.**

And the highest triglyceride tertile at baseline was greater than 250 to less than 1401.

Q **Did the third tertile then contain patients with triglycerides over 500?**

A **Yes.**

Q **Does the table report the hazard ratio for each of the tertiles?**

A **It does.**

Q **And looking at the first tertile, do you see a hazard ratio of?**

A **21.**

Q **That's the relative risk reduction.**

10:16:28 A **Yes, I'm sorry.**

10:16:29 Q **Hazard --**

10:16:30 A **Hazard ratio, .79.**

10:16:34 Q **Sorry, Doctor?**

10:16:35 A **.79.**

10:16:36 Q **Thank you.**

10:16:37 **Looking at the second tertile, does the hazard ratio remain essentially flat or what happens there?**

10:16:41

10:16:43 A **It's flat. It's .80.**

10:16:46 Q **And in the third tertile, do you see a hazard ratio of .67?**

10:16:51

10:16:52 A **Yes.**

10:16:52 Q **And what does that mean in terms of relative risk reduction?**

10:16:55

10:16:56 A **That would be about 32.5 percent.**

10:17:00 Q **And are each of these results statistically significant?**

10:17:04 A **They are all statistically significant.**

10:17:07 Q **And what does this table show about the relationship between the triglyceride levels and cardiovascular risk reduction between and among these different tertiles?**

10:17:10

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10:17:16 A **Well, if you look at the P value in upper right corner it's .33 which is not statistically significant so the conclusion here is that the benefit in each of these tertiles was the same. There isn't a greater benefit in the highest tertile, but all three tertiles do manifest benefit.**

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10:17:37 Q **So are the results obtained with these three different**
10:17:43 **sub populations or three tertiles dependent or independent of**
10:17:49 **their baseline triglyceride levels?**
10:17:51 A **Independent.**
10:17:53 Q **And what does that indicate, if anything, about the**
10:17:57 **relationship between baseline triglyceride levels and whether**
10:18:00 **or not patients derive cardiovascular benefits from Vascepa?**
10:18:04 A **That there was benefit independent of baseline**
10:18:07 **triglycerides.**
10:18:08 Q **Does that mean that regardless of the baseline**
10:18:10 **triglyceride levels, there's benefit?**
10:18:12 A **Yes.**
10:18:12 Q **And from this analysis, what do you conclude about**
10:18:17 **whether patients with very high triglycerides experience**
10:18:21 **cardiovascular risk reduction by being taking Vascepa?**
10:18:26 A **They do. An the FDA agreed with that evaluation as well.**
10:18:29 Q **With Vascepa, after REDUCE-IT, wouldn't there still be**
10:18:36 **some concern that patients with very high triglycerides are**
10:18:41 **going experience this substantial increase, this zoom up in**
10:18:45 **their LDL-C levels that would negate the cardiovascular**
10:18:50 **benefits that are seen in patients with triglyceride levels**
10:18:54 **below 500?**
10:18:55 A **Counsel I'm sorry. Could you repeat that.**
10:18:57 Q **After REDUCE-IT, wouldn't there still have been a concern**
10:19:01 **that patients with very high triglycerides would experience**

10:19:06 this substantial increase in LDL-C that would negate the
10:19:12 cardiovascular benefits that were seen in patients were
10:19:15 triglyceride levels below 500?
10:19:18 A No. And we clearly did not observe that in the REDUCE-IT
10:19:21 trial.
10:19:23 Q And what, if anything did MARINE have to say about
10:19:26 whether that would occur in the 500 and above population?
10:19:31 A MARINE showed that that would not occur.
10:19:34 Q Have the results been published in a peer reviewed
10:19:47 publication?
10:19:48 A For REDUCE-IT?
10:19:49 Q For REDUCE-IT.
10:19:50 A Yes.
10:19:51 MR. ELIKAN: Can we have PX 272.
10:19:57 This is the -- has been previously admitted.
10:20:00 It's the publication by Dr. Bhatt and others.
10:20:04 THE COURT: Thank you.
10:20:05 MR. ELIKAN: Can we turn to page 10, figure 4.
10:20:05 BY MR. ELIKAN:
10:20:13 Q And what's presented here in general terms.
10:20:15 A This is once again a depiction of the endpoint analysis
10:20:19 from the REDUCE-IT trial.
10:20:23 MR. ELIKAN: And I want to direct your attention
10:20:24 to a passage on page 10 in the lower left hand corner. Can we
10:20:30 highlight the sentence "in addition the significantly lower

10:20:34 **risk."**

10:20:34 **BY MR. ELIKAN:**

10:20:40 **Q What do Dr. Bhatt and his fellow authors have to say here?**

10:20:47 **A I quote,**

10:20:47 **"In addition the significantly lower risk of major adverse cardiovascular events with icosapent ethyl than with placebo appeared to occur irrespective of the attained triglyceride level at one year whether it's greater than or equal to 150 or less than 150 milligrams per deciliter, which suggests that the cardiovascular risk reduction was not associated with attainment of a more normal**

10:21:13 **triglyceride level."**

10:21:13 **Q So what, if anything does this have to say about whether patients with very high triglycerides experience cardiovascular risk reduction?**

10:21:17 **A That it didn't matter what your baseline triglyceride level was and, moreover, even if you didn't normalize your triglycerides in a trial, you still derive a benefit.**

10:21:25 **Q In your opinion, will these results from the REDUCE-IT trial have real world implications in the practice of medicine?**

10:21:37 **A They are tremendous real world value in the practice of the medicine, yes.**

10:21:53 Q **Explain.**

10:21:54 A **REDUCE-IT proved that when you take patients already on a statin -- and these patients have remarkably well-controlled LDL, with a mean baseline level of 75, median of 65, and if they have hypertriglyceridemia above 150, there were remarkable reductions in risk in all cardiovascular endpoints evaluated.**

This is a first in clinical trials looking at the use of an adjunct therapy over and above statin in any patient population not just high triglycerides.

Q **And will it have real word implications in treating patients with severe hypertriglyceridemia?**

A **Absolutely.**

Q **You said, I believe, that no triglyceride lowering agent had ever shown these cardiovascular benefits on top of statin therapy; is that right?**

A **That's correct.**

Q **Had any approved triglyceride lowering agent shown such cardiovascular benefits in patients with very high triglycerides?**

A **No, counsel.**

Q **And how is the medical community responded to the REDUCE-IT trial results?**

A **With considerable enthusiasm.**

Q **And has that enthusiastic response been -- has it been**

10:23:30 **reflected in the medical and other literature?**

10:23:33 A **Yes.**

10:23:33 Q **And did you review some of that literature for your work**

10:23:36 **in this case?**

10:23:36 A **I did.**

10:23:38 **MR. ELIKAN: Let's turn to PX 959.**

10:23:38 **BY MR. ELIKAN:**

10:23:43 Q **What is PX 959, Doctor?**

10:23:46 A **It's the editorial by John Kastelein and Erik Stroes that**

10:23:46 **accompanied publication of the REDUCE -IT trial in the *New***

10:23:58 ***England Journal of Medicine*.**

10:23:58 Q **Did you rely on it in forming your opinions?**

10:24:01 A **Yes.**

10:24:03 **MR. ELIKAN: We move for admission of PX 959.**

10:24:07 **MR. KLEIN: No objection.**

THE COURT: 959 is admitted.

(Plaintiffs' Exhibit 959 received in evidence.)

BY MR. ELIKAN:

Q **Let's look at a few passages from this editorial. I'm**

10:24:17 **going to direct your attention to the last paragraph in the**

10:24:17 **left-hand column of the first page, continuing on to the**

10:24:21 **right-hand column.**

10:24:24 **In the first sentence the one beginning "we**

10:24:27 **welcome," how did the authors respond to the REDUCE-IT**

10:24:31 **results?**

10:24:32 A **Drs. Kastelein and Stroes noted "we welcome these results with surprise, speculation, and hope."**

10:24:38 Q **And what do they say was surprising?**

10:24:39 A **"Most surprising was the difference between the results of REDUCE-IT and those of many previous trials of omega-3 fatty acids. A meta-analysis of ten randomized trials involving 78,000 patients did not show that the groups that received omega-3 fatty acids had a lower risk of major adverse cardiovascular events than those receiving placebo, nor did ASCEND," the acronym stands for A Study of Cardiovascular Events in Diabetes, "which tested one gram capsules containing 840 milligrams of Marine omega-3 fatty acids daily in patients, with type 2 diabetes."**

10:24:42 10:24:44 10:24:47 10:24:52 10:24:57 10:25:01 10:25:03 10:25:06 10:25:12 10:25:15 10:25:19 10:25:22

10:25:28 Q **You mentioned a meta-analysis.**

10:25:31 A **Yes.**

10:25:31 Q **What's that?**

10:25:32 A **Well, a meta-analysis is a statistical tool that's used to evaluate complex medical issues where perhaps clinical trials have had difficulty showing a benefit.**

10:25:37 10:25:43

10:25:46 **The advantage of a meta-analysis is that it can take large numbers of patients from many different trials and combine them and come up with an answer, hopefully.**

10:25:49 10:25:53

10:25:59 **MR. ELIKAN: Let's look at one more passage in**

this editorial. Can we pull up the last paragraph of the article on page 2 and highlight the first sentence.

BY MR. ELIKAN:

Q What do the authors note here?

A They conclude,

"After a parade of failed cardiovascular outcome trials of fish oils, REDUCE-IT has shown a substantial benefit with respect to major adverse cardiovascular events."

Q And I want to zero in on that phrase "parade of failed cardiovascular trials of fish oils." What do you understand the authors to mean by the "parade of failed cardiovascular outcome trials of fish oils"?

A Well, we've seen a large number of prospective randomized clinical trials using the omega-3s which have failed.

Q Did you review other commentary elsewhere expressing surprise and enthusiasm for the REDUCE-IT results?

A Yes, counsel.

Q Let's turn to PX 875.

What is PX 875?

A This is an article by Ben Fidler published in September of 2018 entitled, "Amarin Soars As Fish Oil Pill Cuts Risk of Strokes in Long Awaited Study."

Q And did you rely on it in forming your opinions?

A Yes.

10:27:20 MR. ELIKAN: We move for admission of PX 875.

10:27:23 MR. KLEIN: No objection.

10:27:23 THE COURT: 875 is admitted.

10:27:23 (Plaintiffs' Exhibit 875 received in evidence.)

10:27:28 MR. ELIKAN: If we can turn to page 2 and let's a pull up the third and fourth paragraphs.

10:27:30 BY MR. ELIKAN:

10:27:32 Q Do you see a reference to Dr. Norman Lepor?

10:27:36 A Yes.

10:27:36 Q Who is that?

10:27:37 A Norm is a cardiologist at Cedars-Sinai Heart Institute at UCLA in LA.

10:27:37

10:27:45 Q Is he someone you know?

10:27:47 A Yeah.

10:27:47 Q Well-regarded?

10:27:47 A Oh, yeah.

10:27:48 Q Do you see that he says the data are a game changer?

10:27:52 A Yes.

10:27:52 Q What do you understand him to be referring to by the data, that is, what data is he describing as a game changer?

10:27:56

10:28:01 A The REDUCE-IT trial.

10:28:04 Q And looking at the next paragraph, what else does Dr. Lepor have to say?

10:28:08

10:28:09 A Norm says, "The results will impact how I treat patients starting tomorrow."

10:28:13

10:28:14 **MR. ELIKAN: Let's go to page 3 and pull up the**
10:28:18 **top paragraph.**
10:28:18 **BY MR. ELIKAN:**
10:28:21 **Q What else does Dr. Norman Lepor at Cedars-Sinai have to**
10:28:27 **say about REDUCE-IT and Vascepa at the top of the page?**
10:28:30 **A Dr. Lepor says,**
10:28:31 **"The REDUCE-IT results confirm that Vascepa**
10:28:34 **has unique characteristics that will not allow me to**
10:28:38 **extrapolate the results from this trial to other**
10:28:41 **prescribed or over-the-counter fish oils."**
10:28:45 **Q Are there other examples in the literature, commenting on**
10:28:49 **the REDUCE-IT results?**
10:28:50 **A Yes.**
10:28:50 **Q And have you prepared a slide summarizing some of that**
10:28:54 **commentary?**
10:28:55 **A Yes.**
10:28:56 **MR. ELIKAN: Can we have PDX 6-10.**
10:28:56 **BY MR. ELIKAN:**
10:29:00 **Q Can you identify the exhibits referenced in this slide?**
10:29:04 **A Sure. The first is one which quotes Dr. Michael Blaha,**
10:29:10 **in the *New York Times* dated September 2018 and it's PX 0952.**
10:29:17 **The second is one quoting Dr. Prakash, that's**
10:29:21 **P-r-a-k-a-s-h, Deedwania, D-e-e-d-w-a-n-i-a, and this was in**
10:29:31 ***Chest Physician* in November of 2018 and this is PX 0902.**
10:29:37 **The third is one by Dr. Michael Shapiro,**

10:29:41 S-h-a-p-i-r-o, this was a conference call on cardiovascular
10:29:46 drugs in December 2018 and it is PX 0714?
10:29:54 MR. ELIKAN: Your Honor, we move for admission
10:30:00 of PX 952, 902 and 714 into evidence.
10:30:01 MR. KLEIN: No objection, Your Honor. I think
10:30:02 there's an agreement these statements are not being moved in
10:30:05 for the truth of the matter asserted therein. If that's
10:30:08 correct, then no objection.
10:30:09 THE COURT: Is that correct, counsel?
10:30:11 MR. ELIKAN: Yes.
10:30:12 THE COURT: All right. With that qualification,
10:30:14 the three exhibits are admitted, 952, 902 and 714.
10:30:14 (Plaintiffs' Exhibits 952, 902 and 714
10:30:14 received in evidence.)
10:30:14 BY MR. ELIKAN:
10:30:22 Q Can you take us, Doctor, through the commentary reflected
10:30:26 on this slide beginning with the statement of Dr. Michel
10:30:27 Blaha.
10:30:30 A Yeah, Dr. Blaha notes,
10:30:32 "I'm very surprised by the magnitude of the
10:30:35 results which, quite frankly, are large. My
10:30:38 expectations were very low. A lot of people are
10:30:43 legitimately surprised by this."
10:30:46 Q And do you know Dr. Michael Blaha?
10:30:49 A Oh, yeah.
10:30:50 Q I see he's also at the Ciccarone Center; is that right?

10:30:54 A **Yeah, we published a lot of papers together.**

10:30:56 Q **What did Dr. Deedwania have to say in the *Chest Physician* article?**

10:31:02 A **Dr. Deedwania notes,**

10:31:04 **"REDUCE-IT is a phenomenal trial and a game changer because it has shown for the first time that triglyceride reduction with an appropriate therapy, in this case icosapent ethyl, when used in an appropriate doses can make a significant difference."**

10:31:20 Q **And Dr. Shapiro.**

10:31:22 A **"So I think most people in this field would look at this as a homerun and really view this as being an inflection point in our ability to manage atherosclerotic cardiovascular disease risk. We have a new option that impacts cardiovascular outcomes to a greater extent than just throwing on more LDL cholesterol lowering drugs. So now we have a new option for patients in this category who also happen to have elevated triglycerides where you're going to get more bang for your buck by using kind of an orthogonal therapy."**

10:32:02 Q **I asked you about Dr. Blaha, do you also know Dr. Deedwania and Shapiro.**

10:32:08 A **Yes, they're good friends.**

10:32:10 Q **Are they, each of these three individuals well-regarded**

10:32:13 **cardiologists or preventive cardiologists?**

10:32:16 A **Yes.**

10:32:18 Q **Is the commentary that we've been looking at the full**

10:32:21 **extent of praise for the REDUCE-IT results or just examples?**

10:32:25 A **These are examples.**

10:32:31 Q **Let's now turn to the patents and the asserted claims.**

10:32:34 **Have you prepared a slide identifying the claims Amarin is**

10:32:38 **asserting in this case?**

10:32:39 A **Yes, counsel.**

10:32:39 **THE COURT: And I think, counsel, this may be a**

10:32:41 **good time for us to take our morning recess since you are**

10:32:44 **moving to a different topic.**

10:32:47 **We'll take our recess at this time. I -- I**

10:32:50 **don't know if Ms. Vannozzi has advised you of a hearing I have**

10:32:54 **at 1:30 that I need to try to manage. I'll figure out if we**

10:32:59 **should do it in this courtroom or another courtroom, but that**

10:33:03 **hearing I expect will be about 30 minutes.**

10:33:03 **Thank you.**

10:33:03 **(A recess was taken.)**

10:53:57 **THE COURT: Please be seated.**

11:21:36 **Counsel, I apologize, I have to address an**

11:21:39 **emergency matter in our Las Vegas courthouse. It's emergency**

11:21:45 **because there's no power so I had to close the courthouse. I**

11:21:48 **may get interrupted again as we try to evacuate everybody from**

11:21:53 **the building.**

So I apologize.

MR. ELIKAN: May I proceed, Your Honor?

THE COURT: Yes.

MR. ELIKAN: Can we have PDX 6-8, please.

Your Honor, I neglected --

THE COURT: Is one that you wanted to move for admission?

MR. ELIKAN: Yes, I moved in the other one and I received a note saying I hadn't a moved in PDX 6-8 I will rule it under rule --

THE COURT: Any objection?

MR. KLEIN: No objection.

THE COURT: PDX 6-8 is admitted. I had a note to remind you at the end as well, so I'm glad you remembered.

(Plaintiffs' Exhibit 6-8 received in evidence.)

BY MR. ELIKAN:

Q When we were looking earlier, Doctor, at the Tricor and Lovaza demonstratives, I asked you some questions about predictability and I wanted to make sure we were on the same page.

Would a person of ordinary skill in the art in 1998 have expected to see the same elevation of LDL-C when a triglyceride-lowering agent is given to a very high triglyceride population as is seen when a triglyceride-lowering agent is given to a population with

11:23:00 **lower triglyceride levels?**

11:23:02 A **No.**

11:23:03 Q **What, instead, would the person of ordinary skill in the art expect?**

11:23:06 A **They would have expected that with baseline triglyceride above 500, the elevation would have been much steeper, much more substantial compared to less than 500.**

11:23:15 **And, in fact, if we look at patients with triglycerides less than 500, as we saw with fenofibrate label, if they were around 230, they might actually decrease.**

11:23:18 Q **I would like to turn now to the patents and the asserted claims. Have you prepared a slide identifying the claims Amarin is asserting?**

11:23:25 A **Yes.**

11:23:32 **MR. ELIKAN: Can we have PDX 6-11.**

11:23:36 **BY MR. ELIKAN:**

11:23:40 Q **Are these the same claims that Dr. Budoff identified in his testimony?**

11:23:45 A **Yes, counsel.**

11:23:46 Q **And Dr. Budoff testified -- do you recall his testimony, did you review it?**

11:23:47 A **Yes.**

11:23:47 Q **Do you recall that Dr. Budoff testified that use of Vascepa, according to the product label, is covered by these claims. Will you be relying on that testimony today?**

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11:24:17 A **Yes, I will be relying on that testimony.**

11:24:19 Q **Let's cover a few preliminary before we get into the heart of your opinions?**

11:24:23 **Were you instructed about the standard to be used in evaluating whether a patent claim would be obvious.**

11:24:29 A **Yes.**

11:24:31 **MR. ELIKAN: Can we have PDX 6-12, please.**

11:24:31 **BY MR. ELIKAN:**

11:24:37 Q **What are the factors that you were informed must be considered in an obviousness analysis?**

11:24:42 A **There are four. Scope and content of the prior art, differences between the claimed invention and the prior art, level of ordinary skill in the art, and objective evidence of non-obviousness, including unexpected results, long felt need, failure of others, skepticism and praise for or industry recognition of the invention.**

11:25:09 Q **And you just were telling us what's on the left side of the legal standard slide. What do you have on the right there?**

11:25:16 A **A claim may be obvious if a person of ordinary skill in the art who have had, number one, been motivated to combine prior art references to arrive at the claimed invention.**

11:25:28 **And number two, reasonably expected success in making the claimed invention.**

11:25:32 Q **And did you apply the standards that you've just**

testified to and that are displayed on PDX 6-12?

A **Yes.**

Q **In evaluating whether the asserted claims would have been obvious, did you consider the credentials of the person of ordinary skill in the art?**

A **Yes.**

MR. ELIKAN: Can we have PDX 6-13.

BY MR. ELIKAN:

Q **Can you identify the qualifications that you used for the person of ordinary skill in the art?**

A **A clinician with M.D. or DO and at least 2 to 3 years in the experience of diagnosis, evaluation, and treatment of lipid blood disorders including severe hypertriglyceridemia including triglyceride levels of at least 500, or, alternatively, a clinician, such as a nurse practitioner or physician's assistant with 3 to 5 years of experience in the diagnosis, evaluation and treatment of lipid blood disorders including severe hypertriglyceridemia.**

Q **Do you recall that Dr. Heinecke used a different set of credentials for the person of ordinary skill in the art than you did?**

A **Yes.**

Q **Would your opinions that the asserted claims were not obvious be any different if you used the set of credentials that he used instead?**

11:26:48 A **No, counsel.**

11:26:50 Q **And in evaluating whether the claims were obvious, are you using the same March 2008 date that Dr. Heinecke did?**

11:26:55 A **Yes.**

11:26:59 Q **Do you recall that Dr. Heinecke testified that his opinions would not be different if he used the date of February 2009?**

11:27:05 A **Yes.**

11:27:06 Q **Would your opinions also remain the same?**

11:27:06 A **Yes.**

11:27:09 Q **Earlier in this case, the Court construed some of the claim terms in the asserted patents, did you consider and apply those constructions in your analysis?**

11:27:14 A **Yes.**

11:27:17 Q **Among the claim constructions it ruled upon, the Court concluded that "substantially no DHA" means no more than four percent DHA. Do you understand that?**

11:27:20 A **I do.**

11:27:25 Q **And if I use that phrase substantially no DHA, will you understand that I mean no more than four percent?**

11:27:30 A **Yes, counsel.**

11:27:32 Q **I want to turn now to your opinions that the asserted claim were not obvious.**

11:27:33 **Dr. Heinecke testified that the asserted claims would have been obvious over a combination of what he called**

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key prior art references and I want to show you his combination.

MR. ELIKAN: Can we have PDX 6-14.

BY MR. ELIKAN:

Q **And do you agree with Dr. Heinecke's contentions that -- contention that the asserted claims would have been obvious over his proposed combination of what he calls the key prior art Lovaza PDR, Mori 2000, Hayashi and Kurabayashi?**

A **No.**

Q **Let's start with the Lovaza PDR.**

You previously testified the treatment with Lovaza produces a large LDL-C increase in patients with very high triglycerides.

MR. ELIKAN: I want to look at DX 1535, the PDR, at page 3. And can we blow up Table 2 and can we highlight the LDL-C line.

BY MR. ELIKAN:

Q **Is that LDL-C increase reflected in the Lovaza PDR?**

A **Yes.**

Q **And what specifically is the difference between Lovaza and placebo recorded?**

A **For LDL, it's a 44.5 percent increase compared to baseline.**

Q **And adjusted for placebo?**

A **Yes.**

11:29:24 Q **No, no, I'm asking you and what is the number adjusted for placebo?**

11:29:28 A **49.3.**

11:29:29 Q **Is there any statement anywhere in the Lovaza PDR that attributes the rise in LDL-C in severely hypertriglyceridemic patients to either the DHA component alone or the EPA component alone as opposed to the combination of the two and other omega-3 fatty acids in Lovaza?**

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11:29:58 A **No, counsel.**

11:29:59 Q **Let's turn now to Mori 2000, DX 1538.**

11:30:13 **And looking at page 1 in the abstract, in the section called Objective, what did Mori report was the purpose of the study that's discussed in the article?**

11:30:16

11:30:22

11:30:26 A **The study's aim was to determine whether EPA and DHA had differential effects on serum lipids and lipoproteins, glucose and insulin in humans.**

11:30:31

11:30:31

11:30:40 Q **I want to look right below that to the section entitled Design. Can you briefly describe the design of the study in Mori.**

11:30:43

11:30:48

11:30:48 A **It's a double-blind, placebo-controlled trial of parallel design including 59 overweight nonsmoking mildly hyperlipidemic men who were randomly assigned to receive four grams of purified EPA, DHA, or olive oil, which served as the placebo daily while continuing their usual diets for six weeks.**

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11:31:13 Q **Did you say mildly hyperlipidemic?**

11:31:17 A **Yes.**

11:31:18 Q **What does that description indicate about whether Dr. Mori believed he was reporting results relating to treatment of patients with severe hypertriglyceridemia?**

11:31:26 A **Well, he clearly was not treating patients with severe hypertriglyceridemia.**

11:31:31 Q **And were the 59 subjects that you mentioned divided into smaller groups or treated all together?**

11:31:39 A **They were divided into three separate groups.**

11:31:43 **MR. ELIKAN: Let's turn to Table 2 at page 4. Can we highlight the title.**

11:31:46 **BY MR. ELIKAN:**

11:31:51 Q **What type of information is in this table?**

11:31:53 A **This is a summary of the fasting serum lipids, glucose and insulin at baseline and postintervention in the three groups.**

11:32:03 Q **And do you see at the top of the treatment columns in Table 2, what's reported there about how many study subjects were in the different treatment arms of the study?**

11:32:15 A **There were 20 in the olive oil control group, 19 in the EPA group and 17 in the DHA group.**

11:32:23 Q **How would you characterize the size of a study arm with 19 subjects?**

11:32:29 A **It would be considered small.**

11:32:31 Q **Now, Table 2 reports several values including triglycerides and LDL-C levels, right?**

11:32:37 A **Yes.**

11:32:40 Q **In what unit of measurement does Mori report these values?**

11:32:41 A **This is a paper from Australia and there they use millimoles per liter.**

11:32:45 Q **Have you converted the LDL-C and triglyceride values reported in Mori from millimoles per liter to the milligrams per deciliter that we've been talking about at trial?**

11:32:54 A **Yes.**

11:33:00 **MR. ELIKAN: Can we have PDX 6-15.**

11:33:02 **BY MR. ELIKAN:**

11:33:03 Q **What did Mori report was the effect on the LDL-C levels in the patients taking EPA and DHA between baseline and postintervention?**

11:33:09 A **A three-and-a-half percent increase in the EPA group that was not statistically significant and an eight percent rise in the DHA group that was statistically significant.**

11:33:13 Q **And as far as the numbers in milligrams per deciliter are concerned, what was the shift in EPA from baseline to postintervention?**

11:33:20 A **LDL increased from 166 to 17, milligrams per deciliter.**

11:33:32 Q **And in the DHA arm?**

11:33:36 A **LDL increased from 165 to 179 milligrams per deciliter.**

11:33:41

11:33:42

11:33:48

11:33:50

11:33:55 Q **So did both raise LDL-C?**

11:33:58 A **Numerically they both increased.**

11:34:01 Q **And what were the baseline triglyceride levels of patients who received EPA and DHA in Mori 2000 when expressed in terms of milligrams per deciliter?**

11:34:12 A **178 milligrams per deciliter. And the DHA group was 199 milligrams per deciliter.**

11:34:20 Q **And the 178 you mention is for the EPA group?**

11:34:23 A **Yes.**

11:34:27 Q **And were those patients I just want to make sure I'm clear with severe hypertriglyceridemia?**

11:34:33 A **No, counsel.**

11:34:34 Q **Would a person of ordinary skill in the art in 2008 nevertheless have understood that the magnitude of LDL-C increases reported in these patients would be applicable to patients with very high triglycerides?**

11:34:49 A **No, counsel. These are borderline high triglyceride patients, and we've already established that the patients with very high triglycerides have a very different LDL response.**

11:35:00 Q **So I believe you characterize the sample size at least in the EPA arm as small, right?**

11:35:11 A **Yes.**

11:35:12 Q **How do the baseline triglyceride levels of the group taking EPA compare with the group taking DHA?**

11:35:18 A **It's lower. The baseline for EPA is 21 milligrams per**

deciliter lower in the EPA group compared to the DHA group.

Q So the person of ordinary skill in the art I take it would have seen that while there's numerical, I think that's the word you used, increase in LDL-C in both arms only in the DHA arm was the difference significantly significant?

A Yes, sir.

Q Would the person of ordinary skill in the art have attributed this difference to the intrinsic properties of EPA or instead to other issues like sample size or difference in baseline triglyceride levels between the two groups?

A It would have been the latter.

MR. ELIKAN: I want to ask you about a few more passages in Mori. Could we turn to page 3, in the section about serum lipids in the right hand column. Can we highlight the fifth sentence in that paragraph.

BY MR. ELIKAN:

Q What triglyceride reductions did Mori report with EPA and DHA?

A The EPA group experienced an 18.4 percent reduction in triglycerides and the DHA group experienced a 20 percent reduction in triglycerides compared to placebo.

Q And looking at this sentence, would the person of ordinary skill in the art in March 2008 have believed that EPA offered an advantage over DHA in terms of triglyceride lowering?

A **No.**

Q **And more generally, looking at the article as a whole, would a person of ordinary skill in the art viewed Mori as teaching that EPA had advantages over DHA?**

A **No.**

Q **Let's look at some other passages in Mori. I want to go to page 4, the right-hand column under Discussion.**

In the first sentence, do you see that Dr. Mori states that the study addressed whether purified EPA and DHA have different effects on serum lipids and lipoproteins, LDL particle size, glucose and insulin in mildly hyperlipidemic men?

A **Yes.**

Q **And is that, indeed, what the study addressed?**

A **Yes.**

Q **Okay. I want to highlight the second sentence.**

Of the effects studied, what does Mori report about the relative performance of EPA and DHA?

A **We found that DHA, but not EPA improved serum lipid status, in particular a small increase in HDL cholesterol and a significant increase in the HDL2 cholesterol sub fraction without adverse effects on fasting glucose concentrations.**

Q **In plain English what are they reporting there, the authors of this paper?**

A **Well, at the priority date HDL cholesterol was believed**

11:38:30 to be the good cholesterol. The anti-atherogenic cholesterol
11:38:36 and it was believed that raising HDL cholesterol --
11:38:39 Q More generally doctor, are the authors saying that EPA
11:38:45 has advantages over DHA or not?
11:38:47 A Yes.
11:38:49 Q I'm sorry I asked whether EPA is reported as showing
11:38:53 advantages over DHA.
11:38:55 A No. They specifically state that DHA but not EPA
11:39:04 improved serum lipid status.
11:39:06 Q And how did you understand the authors saying that
11:39:11 increases in these parameters with DHA improved serum lipid
11:39:18 status?
11:39:18 A In March of 2008, it would have been viewed as a
11:39:23 positive, if the HDL cholesterol level rose and specifically,
11:39:27 at the time, in general, the HDL-two cholesterol sub fraction
11:39:32 was viewed as the most beneficial sub fraction of HDL. So
11:39:36 this would have been viewed in a positive light.
11:39:40 Q Now, earlier we saw that LDL-C increased by 33.5 percent
11:39:45 -- I'm sorry, let me say that again. By 3.5 percent in the
11:39:50 EPA arm and by eight percent in the DHA arm. In view of that
11:39:55 difference, how do you make sense of Dr. Mori's conclusion
11:39:59 that DHA, but not EPA improved serum lipid status?
11:40:06 A Well, he, here, notes the changes in HDL cholesterol and
11:40:11 HDL-two cholesterol. They had an equal capacity to reduce
11:40:17 triglycerides. Then he goes on to talk about other

advantages.

Q Do you regard this sentence as treating the overall serum lipid status?

A Yes.

Q So given that, and given the difference between the LDL-C performance in the two arms, how do you make sense of his conclusion that DHA but not EPA improved serum lipid status?

A Well, there's also an imbalance in the baseline triglyceride level of 21 milligrams per deciliter, and I think a POSA would have viewed that as enough to perhaps induce a favor to EPA in terms of overall magnitude of LDL elevation. A 21-milligram per deciliter difference could possibly account for whether or not there was a statistically significant difference or not in the EPA group.

Q Would Dr. Mori's conclusion that DHA but not EPA improved serum lipid status have led a person of ordinary skill in the art in March 2008 to get rid of the DHA and use highly purified EPA?

A No.

MR. ELIKAN: Let's turn to page 8. And I want to look at the third full paragraph of the left-hand column. Can we highlight the first sentence.

BY MR. ELIKAN:

Q What did Mori report here about the effects of DHA and EPA on fasting glucose?

11:42:04 A **They both increased fasting insulin but only the EPA**
11:42:10 **increased fasting glucose.**
11:42:11 Q **And would fasting glucose have been of significance, of**
11:42:15 **import to the person of person of ordinary skill in the art in**
11:42:19 **March 2008?**
11:42:19 A **Yes, we don't like to see that.**
11:42:22 Q **Why?**
11:42:22 A **Because it could be a manifestation of insulin**
11:42:26 **resistance. We know that glucose levels when they're**
11:42:30 **increased have adverse effects on arterial walls. They can**
11:42:34 **also contribute to the development of atherosclerotic disease**
11:42:38 **by activating specific pathways. So it's not something we**
11:42:42 **would -- we would think was a good change.**
11:42:45 Q **Are there particular types of patients in whom this would**
11:42:49 **be seen as -- of greater importance?**
11:42:53 A **Yes, patients with metabolic syndrome, prediabetics and**
11:42:59 **then patients who have established diabetes.**
11:43:02 Q **Are many severely hypertriglyceridemic patients diabetic?**
11:43:06 A **A good percentage are, yes.**
11:43:08 Q **And are a good percentage prediabetic?**
11:43:11 A **Yes because high triglycerides were a defining feature of**
11:43:18 **metabolic syndrome which was an indicator of insulin**
11:43:22 **resistance or pre diabetes.**
11:43:25 Q **Would an increase in fasting glucose levels have been of**
11:43:28 **concern in the treatment of diabetics with severe**

hypertriglyceridemia?

A **Surely.**

Q **And why would that be?**

A **Because we don't want to do anything that's going to antagonize glucose control. Controlling glucose within specific boundaries is a component of guidelines around the world.**

Q **Would Mori's conclusion that only EPA increased fasting glucose have somehow motivated the person of ordinary skill in the art in 2008 to get rid of the DHA and use highly purified EPA?**

A **No.**

MR. ELIKAN: I want to turn to page 6, and the last paragraph and highlight the first sentence.

BY MR. ELIKAN:

Q **Do you see a reference to LDL particle size?**

A **Yes.**

Q **What is that?**

A **LDL particle size as this phrase denotes, defines numerically the size of LDL particles circulating in the blood.**

Q **As of 2008, March 2008, would the person of ordinary skill in the art have believed that LDL particle size was of import to patient health?**

A **Yes. The Quebec Cardiovascular Study showed that LDL**

particle size was a factor. Larger particles appeared so be less atherogenic, smaller particles more atherogenic.

And there was also evidence that smaller particles would go -- undergo changes such as oxidation that might make them more atherogenic as well. Smaller particles also have greater difficulty being cleared.

Q **So in a nutshell would it be fair larger good, smaller bad?**

A **In, in general way, yes.**

Q **And in this paragraph, what do the authors report about the effect of DHA on LDL particle size?**

A **That DHA reduced LDL particle size after omega-3 fatty acid supplementation.**

Q **Would this suggestion that DHA increased LDL particle size have led the person of ordinary skill in the art in March 2008 to say get rid of the DHA, use highly pure EPA?**

A **No. No. At the time, it was important to try to get a comprehensive inventory of risk factor burden and certainly the changes wrought by DHA would not be ones that you wanted to exclude from a therapy.**

Q **Viewing the article as a whole would the person of ordinary skill in the art have believed it was desirable to get rid of the DHA and use highly purified EPA in patients with very high triglycerides?**

A **No, and Mori certainly does not signal that conclusion.**

11:46:43 Q **And we've already addressed that Mori addressed mildly hyperlipidemic patients, not the severely hypertriglyceridemic. Does Mori teach that DHA has beneficial properties over EPA or the other way around?**

11:47:03 A **Mori teaches that DHA as beneficial properties that exceed those of EPA.**

11:47:10 Q **And in light of that would the person of ordinary skill in the art want to get rid of the DHA?**

11:47:14 A **No.**

11:47:15 Q **Let's turn --**

11:47:15 A **It would be not be a logical choice.**

11:47:18 Q **I'm sorry I missed that.**

11:47:19 A **It would not be a logical choice.**

11:47:22 **MR. ELIKAN: Let's turn now to Hayashi DX 1532. This is one the other references relied on by Dr. Heinecke in his key prior art combination. I want to go to page 4 and highlight the first sentence of the section titled patients and methods.**

11:47:40 **BY MR. ELIKAN:**

11:47:47 Q **In that sentence what do the authors report was the subject of the study?**

11:47:51 A **The efficacy of ethyl icosapentate in the treatment of 28 patients with FCH, which is familial combined hyperlipidemia and no other health problems or conditions was assessed.**

11:48:06 Q **And ethyl icosapentate is EPA?**

A **Yes.**

Q **And what is FCH?**

A **Familial combined hyperlipidemia is a state where both LDL cholesterol and triglycerides are increased.**

Q **And I want to turn to the fourth sentence of the paragraph, the one beginning with "in the six-week period."**

A **Yes.**

Q **What do the authors state here about the required baseline levels for inclusion of patients in the study?**

A **They note in the six-week period before the start of the study, a serum triglyceride concentration higher than 150 milligrams per deciliter or serum total cholesterol concentration higher than 220 milligrams per deciliter had to be maintained despite the dietary and lifestyle modifications during that six-week period.**

Q **You said or. Is it sufficient to qualify and be included in the study if you meet only one of those or do you have to meet both of the lipid requirements?**

A **One or the other.**

Q **In this paragraph, is there any statement that any subject in the study had triglycerides of at least 500?**

A **No.**

Q **And still in the same paragraph, looking at the penultimate sentence what does the paragraph state was the daily does of EPA studied?**

11:49:39 A **1800 milligrams -- excuse me, 1.8 grams daily.**

11:49:46 Q **Does the patient and methods -- patients and methods section that we're looking at indicate that the study was blinded?**

11:49:52

11:49:53 A **No.**

11:49:54 Q **And based on your review, was it?**

11:49:57 A **No.**

11:49:57 Q **Was the study placebo-controlled?**

11:50:00 A **No.**

11:50:00 Q **How many arms were in the study?**

11:50:03 A **One.**

11:50:05 Q **So it wasn't blinded or placebo-controlled, right?**

11:50:10 A **No.**

11:50:11 Q **Would the person of ordinary skill in the art have believed that these study design characteristics impact the reliability of the results reported?**

11:50:13

11:50:17

11:50:19 A **The scientific method does require that there be a control. And randomized studies are, of course, better.**

11:50:23

11:50:31 Q **I want to turn to the section on page 5 of Hayashi titled Results and highlight the first line.**

11:50:37

11:50:40 **What was the duration of the study, how long?**

11:50:43 A **Eight weeks.**

11:50:44 Q **Let's go to Table 1. What did this table report about the effects of EPA on triglycerides?**

11:50:50

11:50:54 A **That they decreased by 41 percent in a statistically**

significant way with a P value less than 0.05 compared to baseline.

Q And you said statistically different. How do you know that?

A Because there's a cross next to the 41 in the column denoted mean change percent.

Q And turning to LDL-C, what did Table 1 report about the effect of EPA on LDL-C after eight weeks?

A There was a nonstatistically significant 7 percent reduction.

Q Does this table provide any breakdown of LDL-C effects by baseline triglyceride level?

A No.

Q Does it report results for any subjects with very high triglycerides, individual subjects?

A No. No.

Q Would a person of ordinary skill in the art in 2008 have understood that the LDL-C results reported in this title would be informative as to the LDL-C effects in patients with very high triglycerides?

A No.

Q Do you recall that Dr. Heinecke testified that Hayashi included at least one subject with triglyceride levels of at least 500?

A Yes.

11:52:16 Q **In your opinion, would that have been clear to the person of ordinary skill in the art in March 2008?**

11:52:22 A **Not even remotely.**

11:52:23 Q **I want to direct your attention to Figure 2 on page 7.**

11:52:24 **In the legend at the bottom of the figure, what does Hayashi state is covered by these three graphs?**

11:52:32 A **He is evaluating the correlations between the activities of two coagulation factors, 7 and 10, and also plasminogen activator inhibitor one, and he's correlating these with plasma triglycerides at baseline week zero.**

11:52:36 Q **And what's reported on the Y axis of these three figures?**

11:52:39 A **In the topmost figure it is coagulation factor seven, in the middle coagulation factor ten. And in the bottom figure pi one or plasminogen activator inhibitor one.**

11:52:43 Q **And what's reported on the X axis in these three graphs?**

11:52:51 A **Serum triglyceride levels.**

11:52:59 Q **At what week?**

11:52:59 A **At baseline week zero.**

11:53:03 Q **What do the dots in Figure 2 represent?**

11:53:08 A **Those are the values of individual patients.**

11:53:15 Q **Is there any indication on these graphs that show dots for individual patients that any of the study subjects had triglyceride levels of at least 500?**

11:53:21 A **No, counsel. As I go from the top to the bottom, the topmost figure, it appears that the highest triglyceride was**

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425. For the middle figure, it was approximately 375. For the bottom figure it was once again approximately 375.

Q And what's the highest number of subjects reported in these three graphs?

A In the uppermost graph 25. In the middle graph, 22. And in the bottom-most graph 24.

Q So the highest number's in the top graph?

A Yes.

Q And of the 25 subjects whose triglyceride levels are reported in the top graph, is it -- based on your review there is none that exceed 500. How many exceed 400?

A In the topmost graph one exceeds 400. And no one exceeds 400 in the middle or the bottom graph.

Q And in terms of the plot points, the dots that are listed, how many of the values in the top graph exceed 350?

A It appears to be two, in the middle graph, one, and in the bottom graph one.

Q And where are most of the triglyceride values for the subjects in these three graphs concentrated?

A It would be between 150 and 300 or so. Yeah. Some are above. But in terms of were they concentrated, 150 to may be 350.

Q Now, earlier you said that Hayashi studied 28 subjects. But in Figure 2 the largest number was 25.

A Yes.

11:55:48 Q **Does Hayashi identify what the baseline triglyceride**
11:55:53 **levels were of the remaining three subjects?**
11:55:55 A **No, counsel.**
11:55:57 Q **Does Hayashi provide any discussion of why the three**
11:56:03 **triglyceride values aren't reported in this figure?**
11:56:05 A **No.**
11:56:06 Q **Does Hayashi report that the three missing triglyceride**
11:56:11 **values exceeded 500?**
11:56:14 A **No.**
11:56:14 Q **Let's go back to Table 1 on page 5.**
11:56:25 **Do you recall that -- I think I already asked you**
11:56:28 **this but I'm going to ask you again.**
11:56:31 **Do you recall that Dr. Heinecke testified that at**
11:56:33 **least one subject would have had triglyceride levels over 500**
11:56:38 **given that the reported triglyceride mean in Hayashi was 300**
11:56:44 **plus or minus 233 milligrams per deciliter?**
11:56:48 A **Yes.**
11:56:49 Q **And do you agree with him?**
11:56:52 A **No.**
11:56:54 Q **Why not?**
11:56:56 A **Well, where are these patients over 500? A POSA is not**
11:57:02 **going to sit down and begin imputing where that patient is.**
11:57:07 **They're not shown in any of the figures, and, moreover,**
11:57:13 **Hayashi used the Friedewald equation --**
11:57:16 Q **We'll get to the Friedewald equation in a minute, Doctor.**

Let me ask you this. Even if Hayashi enrolled a few subjects with triglyceride levels of at least 500, would it have provided the person of ordinary skill in the art in 2008 with meaningful information about the LDL-C effects of EPA in a population with very high triglycerides?

A **No.**

Q **I want to direct your attention and highlight the last sentence of the first paragraph on page 5.**

Does this sentence reference the Friedewald method that you just testified about?

A **It does, counsel.**

Q **And what does it say?**

A **It states LDL cholesterol concentration was calculated by the Friedewald equation.**

Q **What's the Friedewald equation in general terms?**

A **Well, the Friedewald equation is used to estimate LDL cholesterol levels because they're typically not measured in a lot of these studies directly through an assay.**

So you basically use the total cholesterol, the HDL cholesterol and triglycerides divided by five to estimate the LDL cholesterol.

But the Friedewald is invalid --

Q **Let me ask you this. Do you recall that Dr. Heinecke testified that the Friedewald equation is not a useful tool for measuring LDL-C in patients with triglyceride levels of**

400 milligrams per deciliter or greater?

A **Yes.**

Q **Do you agree with Dr. Heinecke?**

A **Yes, he's correct.**

Q **As of March 2008, was it widely recognized that this Friedewald equation was not a reliable way to estimate LDL-C in patients with very high triglycerides?**

A **Yes, Dr. Friedewald himself pointed it out in the mid '70s.**

MR. ELIKAN: I want to look at DX 1546, the 1998 Saito reference that Dr. Heinecke testified about. And I want to go to page 7.

Can we zoom in on the title Serum Lipid Examination, and bring up the second paragraph under that heading, and can we highlight the third sentence.

Just the third sentence, Mr. Brooks.

BY MR. ELIKAN:

Q **What does Saito in this 1998 article report about the use of the Friedewald equation?**

A **Dr. Saito notes that serum LDL cholesterol was calculated by the below listed formula of Friedewald, although this formula can't be applied when the triglyceride value is greater than or equal to 400 milligrams per deciliter, and such instances were treated as missing data without performing the calculation.**

12:00:25 Q **Returning to Hayashi, as of March 2008, would it have**
12:00:30 **provided a reasonable expectation that using highly purified**
12:00:35 **EPA with substantially no DHA would lower triglycerides**
12:00:40 **without a substantial increase in LDL-C in patients with very**
12:00:45 **high triglycerides?**
12:00:46 A **No.**
12:00:47 Q **And why?**
12:00:53 A **Because he has no demonstrable patients or participants**
12:00:59 **in the study who had triglycerides of 500 or more and**
12:01:04 **moreover, even if he did, the LDL that he would have estimated**
12:01:09 **with the lipid profile in such a patient would be invalid.**
12:01:12 Q **And stepping back did Hayashi study a population were**
12:01:19 **very high triglycerides?**
12:01:21 A **No.**
12:01:22 Q **And what bearing, if any, does that have on the answer to**
12:01:25 **my question about what one would reasonably expect?**
12:01:29 A **The bearing is very simple, it doesn't answer the**
12:01:33 **question. It has no means by which to answer the question.**
12:01:38 Q **And based on Hayashi, if EPA had been given to patients**
12:01:47 **with severe hypertriglyceridemia, a patient population based**
12:01:51 **on the other literature that you've reviewed, looking at it in**
12:01:57 **March 2008, what would they have expected to see in a patient**
12:02:01 **population with very high triglycerides?**
12:02:03 A **That the LDL would have shot up.**
12:02:06 **MR. ELIKAN: Let's go to Kurabayashi. That's**

12:02:07 **the final reference in Dr. Heinecke's key prior art**
12:02:12 **combination. And I want to go to page 1 and put on the screen**
12:02:18 **the first paragraph of the method section in the left-hand**
12:02:21 **column.**
12:02:21 **BY MR. ELIKAN:**
12:02:25 **Q What does Kurabayashi have it say about the design of the**
12:02:28 **study?**
12:02:29 **A Dr. Kurabayashi notes that they performed a prospective**
12:02:34 **observational 48-week study in hyperlipidemic menopausal**
12:02:40 **women. They randomly assigned 141 women whose levels of serum**
12:02:44 **total cholesterol would 220 to 280 milligrams per deciliter or**
12:02:48 **whose serum triglycerides were 150 to 400 milligrams per**
12:02:53 **deciliter.**
12:02:54 **Q Let me stop you right there. I've got a question.**
12:02:57 **So this is the way that hyperlipidemic is defined**
12:03:04 **here?**
12:03:04 **A Yes, in Japan.**
12:03:05 **Q And what were the study groups treated with?**
12:03:10 **A There were two arms. The patients could be treated with**
12:03:15 **either estriol which is an estrogen derivative at two**
12:03:20 **milligrams daily. 72 women were in that group. Or, they**
12:03:25 **could be treated with a combination of ethyl icosapentate**
12:03:32 **which is EPA, at 1.2 grams with two milligrams of estriol, and**
12:03:37 **that group had 69 women.**
12:03:40 **Q So do both of arms get the estriol?**

12:03:43 A **Yes.**

12:03:43 Q **Then turning to page 4, Table 2, what did Kurabayashi report was the mean triglyceride level at baseline of the group that received the EPA and estriol?**

12:03:47 12:03:53 12:03:56 A **135.6, plus or minus 56.9 milligrams per deciliter.**

12:04:04 Q **Would a person of ordinary skill in the art in March 2008 have understood 135 to represent even an elevated triglyceride level?**

12:04:07 12:04:13 12:04:14 A **No. That would have been considered a normal triglyceride level.**

12:04:17 12:04:18 Q **Would a person of ordinary skill in the art in March 2008 have expected that LDL-C effects reported in patients with mean triglycerides of 135 would apply, be translatable to patients with at least 500?**

12:04:22 12:04:27 12:04:36 A **No.**

12:04:38 Q **Why not?**

12:04:38 12:04:40 A **Because they would have known that a group of patients with normal triglycerides would not behave in the same way as a group of patients with very high triglycerides. They would have anticipated a very large rise in LDL but with normal triglyceride as in this range perhaps they would have even seen a drop in LDL.**

12:04:44 12:04:52 12:04:55 12:04:59 12:05:03 Q **Was there an arm in Kurabayashi that studied DHA?**

12:05:04 A **No.**

12:05:09 Q **Now, we've established that the arms in the study**

12:05:10

12:05:17 **received estriol. What is estriol?**

12:05:20 A **Estriol is a downstream metabolite of estrogen. And**

12:05:26 **estriol is bioactive and it has effects on lipids, all**

12:05:32 **estrogens do.**

12:05:34 Q **Would the person of ordinary skill in the art in**

12:05:38 **March 2008 have known that estriol would have an effect on**

12:05:42 **lipid levels?**

12:05:42 A **Yes.**

12:05:43 Q **Given that belief, would the person of ordinary skill in**

12:05:53 **the art, reading Kurabayashi in March 2008, have drawn any**

12:05:59 **conclusions about the lipid effects of EPA alone?**

12:06:04 A **No. Because there was no EPA mono therapy arm of the**

12:06:08 **study.**

12:06:09 Q **Do you recall that Dr. Heinecke testified that estriol**

12:06:13 **does not interact with EPA and that therefore the presence of**

12:06:17 **estriol in both arms of the study did not confound the effects**

12:06:21 **of EPA?**

12:06:22 A **You can't draw that conclusion --**

12:06:22 Q **I know --**

12:06:24 A **-- from these data.**

12:06:25 Q **Okay. So you disagree with his testimony?**

12:06:29 A **I do.**

12:06:29 Q **And why do you disagree with Dr. Heinecke?**

12:06:37 A **Because the cleanest way to determine that would be to**

12:06:40 **also have included an EPA monotherapy arm.**

12:06:44 Q **Is estrogen something that you've studied or had to deal with during your ob-gyn training?**

12:06:48 A **Of course.**

12:06:53 Q **Is it a complex or a simple molecule?**

12:06:53 A **It's a complex molecule.**

12:06:56 Q **And how would that affect the analysis of how much this Kurabayashi study tells us, if anything, about the effects of EPA alone?**

12:06:58 A **Yeah, I don't think it tells you much of anything about EPA alone.**

12:07:04 Q **Did Dr. Heinecke cite any prior art or any literature to support his position?**

12:07:08 A **No.**

12:07:09 Q **So we've now addressed Dr. Heinecke's key prior art. I want to turn to your opinion that the asserted claims were not obvious, and I want to turn to claim 1 of the '728 patent.**

12:07:12 **Have you prepared a slide that summarizes the general reasons for your opinion that claim 1 would not have been obvious?**

12:07:13 A **Yes, counsel.**

12:07:19 **MR. ELIKAN: Can we have PDX 6-16.**

12:07:19 **BY MR. ELIKAN:**

12:07:24 Q **And can you identify the general bases for your opinion.**

12:07:28 A **There was no reasonable expectation that high purity EPA would avoid substantial increases in LDL cholesterol in**

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12:07:57 **patients with very high triglycerides.**

12:07:59 **DHA was thought to be better for lipid and**
12:08:02 **cardiovascular effects than EPA, and a POSA therefore would**
12:08:07 **not have been led to use high purity EPA and substantially no**
12:08:12 **DHA.**

12:08:12 **There was not a finite number of predictable options**
12:08:18 **to pursue if seeking to lower triglycerides without**
12:08:20 **substantially increasing LDL cholesterol in patients with**
12:08:24 **severe hypertriglyceridemia and no reasonable expectation of**
12:08:27 **success, and then there were objective indicia of**
12:08:32 **nonobviousness.**

12:08:33 Q **When you said POSA is that an acronym for person of**
12:08:38 **ordinary skill in the art?**

12:08:38 A **Yes.**

12:08:38 Q **I want to explore each of these points more fully. Let's**
12:08:43 **start with the first.**

12:08:44 **Do you recall that Dr. Heinecke testified that a**
12:08:47 **person of ordinary skill in the art would have reasonably**
12:08:50 **expected that one could avoid the large LDL-C increases**
12:08:55 **reported in the Lovaza PDR by replacing the EPA, DHA, omega-3**
12:09:06 **fatty oil mixture with a more highly purity EPA formulation?**

12:09:10 A **Yes, I recall.**

12:09:10 Q **I'm sorry?**

12:09:11 A **I recall.**

12:09:12 Q **Do you agree with him?**

12:09:16 A **No.**

12:09:16 Q **Why not?**

12:09:17 A **Because we have seen no evidence that it's DHA as opposed to EPA that is responsible for the elevation in LDL.**

12:09:22 **And moreover, in Lovaza, it's not just a simple mixture of EPA and DHA, it's actually a much more complex mixture which they call omega-3 acid ethyl esters. There's 80 milligrams worth of other omegas in that preparation.**

12:09:28 **So, no, it was not obvious.**

12:09:45 Q **And would the person of ordinary skill in the art looking at Lovaza have blamed the LDL-C rise observed in treating patients with very high triglycerides on the particular drug or, instead, on what happens when you lower triglycerides in that population?**

12:09:47 A **The mechanism for lowering triglycerides in that population.**

12:09:52 Q **Explain.**

12:09:57 A **Well, all of the drugs that had been approved for the management of severe hypertriglyceridemia had a common theme for patients in that boat. All of the drugs reduced the LDL triglycerides and induced a triglyceride elevation that was proportional to the baseline triglyceride.**

12:10:00 **I believe -- did I say LDL elevation?**

12:10:04 **THE COURT: Yes.**

12:10:06 **THE WITNESS: LDL -- excuse me, court reporter.**

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That would induce an LDL-C elevation that was proportional to the magnitude of the baseline triglyceride. So they would have believed it was actually a physiologic mechanism by which VLDL is converted to LDL.

BY MR. ELIKAN:

Q **Was there suggestion in the prior art that one could avoid large LDL increases in patients with very high triglycerides by changing the composition of Lovaza to include substantially all the omega-3 fatty acids except EPA?**

A **No.**

Q **Do you recall that Dr. Heinecke testified that he doesn't think there's any evidence in the prior literature about what the impact of EPA would be on LDL cholesterol in patients with triglycerides above 500 milligrams per deciliter?**

A **Yes.**

Q **Without such evidence, was there any basis for a person of ordinary skill in the art to expect to see no LDL-C effect when EPA is given to patients with very high triglycerides?**

A **Of course not.**

MR. ELIKAN: I want to look again at PDX 6-7 and 6-8. Can we put those side by side on the screen, Mr. Brooks?

BY MR. ELIKAN:

Q **So you testified earlier about these -- the experience with Lovaza and Tricor, triglyceride lowering agents when given to patients with severe hypertriglyceridemia, right?**

12:12:18 A **Yes.**

12:12:18 Q **Based on that information, would the person of ordinary skill in the art have reasonably expected that you would see the same effects with patients having triglyceride levels above 500 as you would with patients with triglyceride levels below 500?**

12:12:36 A **No.**

12:12:37 Q **Now, you testified earlier that the mean triglycerides in the mildly hyperlipidemic men studied by Mori was 178 in the EPA arm.**

12:12:50 A **Yes.**

12:12:51 Q **Looking at these slides, with which group would the population of mildly hyperlipidemic men studied in Mori best fit?**

12:13:02 A **That would be the one to the far left.**

12:13:04 Q **Of which of the --**

12:13:06 A **Of the left plot. So that would be the Tricor group with mixed dyslipidemia with triglycerides over 150 but mean of 231.9.**

12:13:18 Q **Are you aware of any prior art that taught EPA would perform differently from DHA in terms of LDL-C effects in patients with triglyceride levels of at least 500?**

12:13:33 A **Counsel, please repeat that.**

12:13:34 Q **Are you aware of any prior art -- so before March 2008 -- that taught EPA would perform differently from DHA in terms of**

12:13:45 **LDL-C effects in patients with triglyceride levels of at least**
12:13:50 **500?**
12:13:51 A **No.**
12:13:51 Q **As of March 2008, was there any prior art demonstrating**
12:14:00 **that EPA had a different mechanism of action than DHA for**
12:14:05 **lowering triglycerides?**
12:14:06 A **No.**
12:14:07 Q **You've testified that the fatty acid mixture in Lovaza**
12:14:15 **substantially raised LDL-C in patients with very high**
12:14:19 **triglycerides, right?**
12:14:19 A **Yes.**
12:14:21 Q **As of March 2008 would the person of ordinary skill in**
12:14:24 **the art have had any reason related to mechanism of action to**
12:14:29 **expect that administering EPA by itself to such a population**
12:14:35 **would avoid substantially raising LDL-C?**
12:14:38 A **No.**
12:14:39 **MR. ELIKAN: I want to pull up DDX 6.70 from the**
12:14:43 **slide deck of Dr. Heinecke.**
12:14:43 **BY MR. ELIKAN:**
12:14:48 Q **Now, in his testimony Dr. Heinecke cited add discussed**
12:14:53 **some other references, Saito, 1998, Takaku 1991, Matsuzawa**
12:15:05 **1991 and Nakamura 1999, in which a single subject or a few**
12:15:10 **subjects receiving high purity EPA had triglyceride levels of**
12:15:15 **at least 500. Do you recall that testimony?**
12:15:17 A **Yes.**

12:15:17 Q **Did those references report the LDL-C effects of high purity EPA in such subjects?**

12:15:22 A **No.**

12:15:25 Q **Did any of these references study the effect of a 4-gram dose of EPA?**

12:15:30 A **No.**

12:15:31 Q **I'm sorry?**

12:15:31 A **No.**

12:15:32 Q **Would any of these references have provided the person of ordinary skill in the art in March 2008 with a reasonable expectation of avoiding substantial increases in LDL-C in patients with very high triglycerides?**

12:15:33 A **No, counsel.**

12:15:41 **MR. ELIKAN: Let's look at the Takaku reference that Dr. Heinecke relied upon. That's DX 1550, Mr. Brooks. And can we turn to page 12, Figure 3.**

12:15:49 **In the lower right-hand corner of the chart, if we could highlight that, Mr. Brooks.**

12:15:50 **BY MR. ELIKAN:**

12:15:54 Q **That addresses preadministration serum triglycerides. How many patients were studied when you add up the numbers?**

12:15:59 A **Thirty-three.**

12:16:03 Q **That's the 13 plus six plus four plus two?**

12:16:06 A **Yes, I think my math is correct there, it's 33.**

12:16:08 Q **And looking at the bottom line, what was the mean**

12:16:31 **triglyceride levels studied?**

12:16:33 **A 245 plus or minus 41.**

12:16:36 **Q Do you recall that Dr. Heinecke testified that three of these subjects had triglyceride levels that exceeded 500?**

12:16:42 **A Yes.**

12:16:43 **Q Does the Takaku paper anywhere provide information about the effect of the medication that was administered on LDL-C for those particular subjects?**

12:16:54 **A No.**

12:16:55 **Q I want going to go to page 21 and the paragraph with the heading shift in serum LDL cholesterol.**

12:17:05 **Highlighting the parenthetical in the first sentence, do you see that it indicates that LDL-C results were not obtained -- I'm sorry, that it says -- I'm paraphrasing, but that LDL-C results were not obtained for six subjects.**

12:17:25 **A I see that.**

12:17:26 **Q Did Takaku provide any information about the triglyceride levels of the subjects that were excluded?**

12:17:36 **A No.**

12:17:38 **Q Could they have included the subjects reported to have triglycerides over 500?**

12:17:43 **A I think it would have been scientifically responsible, yes.**

12:17:47 **Q I'm not sure I followed your answer. Let me --**

12:17:53 **A It's very -- I believe it would have been scientifically**

12:17:57 responsible to provide that information so that you can read
12:18:00 the paper and understand which patients were included, which
12:18:04 ones weren't.
12:18:05 Q Okay. So I'm asking about the six excluded subjects.
12:18:08 A Yes.
12:18:08 Q Could they have included the subjects reported to have
12:18:11 triglycerides over 500?
12:18:13 A Absolutely.
12:18:14 Q Does Takaku anywhere disclose clearly what method was
12:18:19 used to measure LDL-C in any of the patients studied?
12:18:23 A No.
12:18:24 Q We talked about Takaku. Did you prepare a slide based on
12:18:29 Dr. Heinecke's slide, 6.70, but that gives the rest of the
12:18:34 story for Takaku and the other references?
12:18:37 A Yes.
12:18:38 MR. ELIKAN: Can we have PDX 6-18.
12:18:38 BY MR. ELIKAN:
12:18:43 Q Can you tell us what you believed were the -- was the
12:18:46 takeaway message from Takaku 1991 that tells the rest of the
12:18:51 story.
12:18:53 A Three of 33 subjects had triglycerides that exceeded 500.
12:18:57 Mean triglyceride for the study was 245.
12:19:01 No LDL cholesterol results provided for patients
12:19:05 with triglycerides over 500, and no method for measuring LDL-C
12:19:10 was clearly disclosed.

12:19:12 Q **Let's turn to Nakamura, on 1439. Can you walk us through what the rest of the story is.**

12:19:18 A **One of 14 subjects had triglycerides that exceeded 500.**

12:19:20 **The mean triglyceride in the study was 183. No LDL-C measurements provided.**

12:19:23 Q **Matsuzawa 1991, the rest of the story.**

12:19:26 A **One of 26 subjects had a triglyceride that exceeded 500. The mean triglyceride for participants was 308. No LDL cholesterol results provided for patients with triglycerides over 500. And fine there were, they used the Friedewald equation to calculate or estimate LDL, which is invalid over 400.**

12:19:30 Q **Saito, what's the rest of the story?**

12:19:33 A **One of 12 subjects had a triglyceride that exceeded 500. Mean triglyceride was 295.**

12:19:37 **No LDL cholesterol results for patients with triglycerides over 500, and even they again used the Friedewald equation to estimate LDL-C.**

12:19:44 Q **Taken together, do you any of these studies -- are any of these studies directed to a patient population with very high triglycerides?**

12:19:46 A **No.**

12:19:51 Q **Do you recall that Dr. Heinecke also discussed the Epadel prescribing information from 2007?**

12:19:55 A **Yes.**

12:20:41 **MR. ELIKAN: Can we have DX 1528. And I want to go to page 1.**

12:20:45 **BY MR. ELIKAN:**

12:20:48 **Q Looking in the upper left-hand corner, what version of the Epadel prescribing information was the 2007?**

12:20:55 **A Version 5 released in January of 2007.**

12:20:58 **Q And turning to the second page, I want to turn to the section indications efficacy?**

12:21:05 **A Yes.**

12:21:06 **Q What's the first indication listed here?**

12:21:10 **A Arteriosclerotic ulceration, alleviation of pain, and feeling of cold.**

12:21:18 **Q Does that have anything to do with elevated triglycerides, that indication?**

12:21:22 **A The feeling of cold or all three?**

12:21:25 **Q Okay. Put together, it's one indication, is that indication about hypertriglyceridemia or severe hypertriglyceridemia or anything of the sort?**

12:21:37 **A Arteriosclerotic ulceration could be, but that's not easy to establish or diagnose. So I would have to say on balance, no.**

12:21:50 **Q And what's the second indication listed there?**

12:21:54 **A Well, it's this nebulous hyperlipidemia.**

12:22:03 **Q Any definition provided in the Epadel document that we're looking at about what precisely hyperlipidemia means?**

12:22:12 A **No, it's a little bit of a garbage basket term here, and**
12:22:15 **I'm puzzled by that because by now it would have been routine**
12:22:19 **to provide very specific classifications and definitions of**
12:22:22 **what type of hyperlipidemia you're talking about because there**
12:22:27 **was no single drug available anywhere on earth that would**
12:22:31 **treat all forms of hyperlipidemia.**
12:22:33 Q **Looking to the right of hyperlipidemia, do you see the**
12:22:37 **second paragraph states that when an excess of triglycerides**
12:22:42 **are presented, depend on the extent of it, the dosage may be**
12:22:47 **increased to 900 milligrams per time and three times daily.**
12:22:52 A **Yes.**
12:22:52 Q **Does this provide any information about the level of**
12:22:56 **triglycerides that were constitute an excess of triglycerides?**
12:22:59 A **It provides no guidance, and, by this time, ATP III was**
12:23:04 **available, and certainly if you are marketing a drug like**
12:23:07 **this, you would want people to understand what it is you're**
12:23:11 **treating and what the clinical trial data are to support the**
12:23:15 **use of this in that setting.**
12:23:18 Q **Is there anything in this passage that clearly indicates**
12:23:22 **that in obtaining this indication, EPA was administered to**
12:23:26 **patients with triglyceride levels of at least 500?**
12:23:29 A **No.**
12:23:30 Q **Have you seen anything in this document, as a whole, that**
12:23:36 **shows that in obtaining this indication, EPA was administered**
12:23:42 **to patients with triglyceride levels of at least 500?**

12:23:45 A **There's nothing here to indicate that.**

12:23:47 Q **Does the label report any LDL-C effects resulting from the administration of EPA?**

12:24:12 A **No, counsel, there is no reference to LDL-C change.**

12:24:16 Q **Does it even mention LDL-C?**

12:24:19 A **No.**

12:24:20 Q **Does the Epadel prescribing information from 2007 describe the effects of EPA on apo B?**

12:24:30 A **No, sir.**

12:24:31 Q **In any population.**

12:24:32 A **No.**

12:24:33 Q **Does it even mention apo B?**

12:24:36 A **No.**

12:24:38 **MR. ELIKAN: Let's go back to the indication section on the second page, we're already there.**

12:24:39 **BY MR. ELIKAN:**

12:24:43 Q **What did the Epadel prescribing information describe as the dosing for hyperlipidemia? We walked through this a moment ago but I'm going ask you again and I've got a question about this.**

12:24:55 A **There are two recommendations here, 600 milligrams, 3 times daily, which would be 1.8 grams total daily. Dosage can be increased depending upon age and condition. Which, again, what is someone supposed to make of that?**

12:25:17 **And then another dose would be the 2.7 grams dose**

12:25:23 **900 milligrams 3 times daily for an excess of triglycerides**
12:25:28 **which of course is not defined.**
12:25:30 **Q Do you read this as pointing to a 4-gram dose of EPA?**
12:25:35 **A No.**
12:25:35 **Q Let's turn back to PDX 6-19, your summary slide. I'm**
12:25:43 **going to go to the second reason now that claim 1 in your**
12:25:46 **opinion was not obvious.**
12:25:51 **I would like to begin with the references that we**
12:25:53 **looked at before, starting with the Lovaza PDR. So did the**
12:25:58 **Lovaza PDR, DX 1535, suggest there were advantages to using**
12:26:05 **high purity EPA over using DHA?**
12:26:09 **A No.**
12:26:09 **Q Did it suggest there were advantages in using high purity**
12:26:14 **EPA over an EPA-DHA mixture?**
12:26:18 **A No.**
12:26:19 **Q Did the Lovaza PDR draw any comparisons whatsoever**
12:26:24 **between the individual effects of EPA and of DHA?**
12:26:29 **A No.**
12:26:32 **Q Would it have motivated the person of ordinary skill in**
12:26:36 **the art in March 2008, to eliminate substantially all the DHA**
12:26:42 **and instead use only high purity EPA to treat severe**
12:26:48 **hypertriglyceridemia?**
12:26:50 **A Of course not.**
12:26:52 **Q Let's turn to Hayashi.**
12:26:56 **Would Hayashi have led a person of ordinary skill in**

the art in March 2008 to use high purity EPA instead of DHA or a DHA-EPA mixture in patients with very high triglycerides?

A **It offered no basis for such an approach.**

Q **Did it state that high purity EPA had any advantages over DHA?**

A **No.**

Q **Did it compare the effects of high purity EPA to high DHA?**

A **No.**

Q **Let's turn to Kurabayashi.**

Would Kurabayashi have led the person of ordinary skill in the art in March 2008, to use high purity EPA instead of DHA to treat severe hypertriglyceridemia?

A **No. There was no one enrolled in the study with a triglyceride over 400.**

Q **Would it have led the person of ordinary skill in the art in March 2008, to use high purity EPA instead of a DHA-EPA mixture to treat severe hypertriglyceridemia?**

A **No, there was no EPA monotherapy arm and there was also no comparison between EPA and DHA within the study.**

Q **Is there somewhere in Kurabayashi that Kurabayashi states that high purity EPA has advantages over DHA?**

A **No.**

Q **I think we've already been through this. There's no comparison of high purity EPA to DHA in Kurabayashi, right?**

12:28:26 A **No, counsel.**

12:28:27 Q **Let's turn to Mori.**

12:28:41 **Would Mori, PX 1538, have led a person of ordinary skill in the art in March 2008 to use high purity EPA instead of DHA or a DHA-EPA mixture to treat patients with severe hypertriglyceridemia?**

12:28:58 A **No, because even the authors of the paper suggested that there were so many advantages to DHA you wouldn't want to leave it out.**

12:29:07 Q **In view of those advantages, would the person of ordinary skill in the art have wanted to pursue a treatment that avoids DHA?**

12:29:16 A **No.**

12:29:17 Q **In your work on this case, did you consider whether Mori's suggestion that DHA has advantages over EPA was reflected in the prior art as a whole as of March 2008?**

12:29:33 A **Yes.**

12:29:34 Q **And what, as a whole, did the prior art have it say about that?**

12:29:38 A **That there were distinct advantages to the use of DHA over EPA.**

12:29:43 Q **Have you prepared a demonstrative that illustrates different ways in which the prior art suggested DHA may have advantages over EPA in terms of cardiovascular health?**

12:29:57 A **Yes, counsel.**

12:29:58 **MR. ELIKAN: Can we have PDX 6-20.**

12:29:58 **BY MR. ELIKAN:**

12:30:02 Q **And what does this slide illustrate?**

12:30:04 A **This is just a summary schematic showing HDL in the left sphere, and HDL cholesterol at the time was believed to be beneficial if you raised it.**

12:30:16 **In the middle sphere you see LDL particle size which we've discussed, and in the right, most sphere blood pressure.**

12:30:26 Q **And what is the title above?**

12:30:28 A **"Prior Art Suggested DHA Had Advantages Over EPA With Respect to These Factors."**

12:30:33 Q **Okay. I want to discuss these considerations one at a time starting with HDL-C. What is that again?**

12:30:41 A **High density lipoprotein cholesterol, believed to be the good cholesterol.**

12:30:46 **Okay. Pickup truck, so the LDL would be viewed as the dump truck leaving cholesterol and other lipids proximate the blood vessel wall. The HDL particle would be seen as the pickup truck because it could pick up the excess lipid and take it back to the liver for disposal, which would be seen as beneficial.**

12:31:04 Q **You previously testified that Mori reported that DHA but not EPA increased HDL-C. Was there other prior art as of March 2008 saying that DHA raised HDL-C?**

12:31:20 A **Yes.**

12:31:20 Q **I want to turn to --**

12:31:22 **THE COURT: Before you turn to the prior art.**

12:31:25 **MR. ELIKAN: Yes.**

12:31:26 **THE COURT: Counsel, could I have the doctor explain again about this idea of the dump truck and the pickup truck in explaining this diagram. I'm trying to understand. I don't quite understand.**

12:31:38 **MR. ELIKAN: Okay. Would it help, Your Honor, if we went back to the demonstrative that we were looking at earlier about the metabolism of VLDL to LDL?**

12:31:47 **THE COURT: I doubt -- I remember that --**

12:31:50 **THE WITNESS: I can --**

12:31:52 **THE COURT: -- demonstrative. I think I understand that. I just want to understand this one.**

12:31:55 **THE WITNESS: Okay. Your Honor, the HDL lipoprotein is seen as the good cholesterol-bearing lipoprotein because --**

12:32:05 **THE COURT: That's all -- that's usually how I try to remember. H is good, you want high. L is bad, you want low.**

12:32:15 **THE WITNESS: Yeah, yeah.**

12:32:15 **And what the HDL particle can do is it can interact with cell components in the blood vessel wall that are taking up excess cholesterol leading to the formation of an atherosclerotic plaque.**

12:32:29 Well, this is the one lipoprotein that can
12:32:31 actually interact with that, draw cholesterol out, get back
12:32:37 into the bloodstream, and take it back to the liver for
12:32:40 elimination.
12:32:40 THE COURT: Oh, that's what you analogized HDL
12:32:43 as a dump truck taking that back --
12:32:44 THE WITNESS: The pickup truck.
12:32:46 THE COURT: Thank you.
12:32:46 THE WITNESS: And it was shown in studies that
12:32:51 people with higher HDL had lower risk for the development of
12:32:55 heart disease.
12:32:57 So at the time, in March 2008, if you increased
12:33:01 HDL, it would have been seen as a good thing.
12:33:05 THE COURT: Got it. Thank you.
12:33:06 Is it still seen as a good thing now?
12:33:09 THE WITNESS: It is, but some studies have been
12:33:12 negative, but effort is still being made to investigate it
12:33:15 further because it's very complicated.
12:33:18 THE COURT: Thank you.
12:33:19 MR. ELIKAN: I want to turn to DX 1933. This is
12:33:25 a pre-admitted article, Your Honor, by Dr. Agren, titled "Fish
12:33:31 Diet, Fish Oil, and Docosahexanoic Acid Rich Oil Lower Fasting
12:33:39 and Postprandial Plasma Lipid Levels" from 1996, and the
12:33:46 parties have stipulated that it's prior art, and that's in
12:33:51 paragraph 65.

12:33:51 **THE COURT: Thank you.**

12:33:51 **BY MR. ELIKAN:**

12:33:57 Q **I want to look at the objective. What did this**

12:34:01 **publication concern?**

12:34:03 A **The present study was carried out to clarify the effects**

12:34:07 **of fish diet, fish oil, and DHA-rich oil on fasting and**

12:34:14 **postprandial lipid levels in healthy male students.**

12:34:18 Q **What's postprandial?**

12:34:20 A **That's after a meal.**

12:34:23 **MR. ELIKAN: Let's turn to page 6 in the second**

12:34:24 **paragraph under discussion. I want to highlight the two**

12:34:32 **sentences starting Sanders and Hinds.**

12:34:32 **BY MR. ELIKAN:**

12:34:37 Q **What did the authors have to say about DHA here in the**

12:34:43 **Agren article?**

12:34:43 A **Sanders and Hinds found increased HDL and HDL-2**

12:34:49 **cholesterol concentrations after DHA-rich fish oil intake and**

12:34:54 **proposed that DHA is responsible for these changes.**

12:34:57 **The greatest increase of total HDL and HDL-2**

12:35:02 **cholesterol in the DHA oil group in the present study supports**

12:35:06 **this idea.**

12:35:09 Q **So are those results and the observation made here about**

12:35:14 **Sanders and Hinds, is that consistent with what we saw in**

12:35:19 **Mori?**

12:35:20 A **Yes.**

12:35:22 **MR. ELIKAN: Let's go back to PDX 620, and I want to turn now to LDL particle size.**

12:35:27 **BY MR. ELIKAN:**

12:35:32 Q **Did you review other prior art that suggested as Mori did that DHA, but not EPA, increased LDL particle size?**

12:35:37 A **Yes.**

12:35:42 **MR. ELIKAN: Can we have PX 563, please.**

12:35:43 **And, Your Honor, this has been pre-admitted it's article by Woodman, and it's titled "Docosahexanoic Acid But Not Icosapentaenoic Acid Increases LDL Particle Size in Treated Hypertensive Type 2 Diabetic Patients," and the parties have stipulated to it as prior in paragraph 74.**

12:35:48 **THE COURT: 74?**

12:35:51 **MR. ELIKAN: Yes.**

12:35:59 **THE COURT: Thank you.**

12:36:05 **BY MR. ELIKAN:**

12:36:12 Q **Now, is Dr. Mori a coauthor of this article?**

12:36:16 A **Yes, he's a second author.**

12:36:19 **MR. ELIKAN: I want to go to highlight the first sentence in the last paragraph in the left-hand column beginning with "these data."**

12:36:19 **BY MR. ELIKAN:**

12:36:22 Q **What do the authors report here about the relative effects of EPA and DHA on LDL particle size?**

12:36:28 A **They note that the data that they're reporting in this**

12:36:34

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paper supports their previous study in overweight hypercholesterolemic subjects which is the Mori paper from the *American Journal of Clinical Nutrition* which is the Mori that we had been discussing, in whom LDL particle size increased after supplementation with DHA but not EPA.

Q And you were referring to the citation two in the references, Doctor?

A Yes, counsel.

Q And is that the same Mori article that Dr. Heinecke testified about from 2000?

A Yes.

Q Let's look at the last paragraph of the article. So it's in the middle column.

What do the authors conclude about the therapeutic value of DHA as compared to EPA?

A They conclude that supplementation with purified DHA increases LDL particle size, reduces serum triglycerides and increases HDL-2 cholesterol as well as improves vascular function and blood pressure. Therefore, for subjects with type 2 diabetes, DHA may have more therapeutic value than EPA as food additive --

Q So -- oh, I'm sorry.

A -- but longer term prospective studies are needed to address the issue.

Q And were the findings about LDL particle size -- I take

12:38:27 it they're fully consistent with Mori 2000 based on your
12:38:31 analysis of reference to in the citation to?
12:38:35 A They are.
12:38:35 Q All right. I want to go back to PDX 6-20 and move to the
12:38:40 next factor, blood pressure.
12:38:42 As of March 2008, would the person of ordinary skill
12:38:47 in the art have understood that blood pressure was related to
12:38:50 cardiovascular health?
12:38:51 A Oh, yes, all over the world.
12:38:55 Q And why is that? What's the relationship between the
12:39:00 two?
12:39:00 A As blood pressure increases, risk for cardiovascular
12:39:04 disease increases, and in patients with elevated blood
12:39:08 pressure, it's important to reduce the blood pressure to
12:39:11 reduce risk.
12:39:12 Q And what did the prior art have to say about the relative
12:39:15 effects of EPA and DHA on blood pressure?
12:39:19 A That DHA had more favorable effects on blood pressure
12:39:23 than EPA.
12:39:24 MR. ELIKAN: Let's turn to PX 565, which has
12:39:32 been pre-admitted, Your Honor, and the parties have stipulated
12:39:35 to it as prior art and that's in paragraph 76.
12:39:40 THE COURT: Thank you.
12:39:40 BY MR. ELIKAN:
12:39:42 Q And what is PX 565?

12:39:44 A **This is a paper published in the journal *Hypertension* in**
12:39:49 **1999, another paper by Trevor Mori entitled, "DHA But Not EPA**
12:39:55 **Lowers Ambulatory Blood Pressure in Heart Rate in Humans."**
12:40:00 **MR. ELIKAN: And can we highlight the second**
12:40:02 **sentence of the abstract on page 2, Mr. Brooks.**
12:40:02 **BY MR. ELIKAN:**
12:40:13 Q **What was the stated aim of the study?**
12:40:15 A **The aim of the study was to determine whether there were**
12:40:18 **significant differences in the effects of purified EPA or DHA**
12:40:22 **on ambulatory blood pressure and heart rate in humans.**
12:40:28 **MR. ELIKAN: And can we highlight the sentence**
12:40:30 **beginning with purified DHA further down this paragraph.**
12:40:30 **BY MR. ELIKAN:**
12:40:38 Q **What does Mori report here about the relative effects of**
12:40:43 **DHA and EPA on blood pressure?**
12:40:45 A **That purified DHA but not EPA reduced ambulatory blood**
12:40:50 **pressure and heart rate in mildly hyperlipidemic men. The**
12:40:59 **results of this study suggest that DHA is the principal**
12:40:59 **omega-3 fatty acid in fish and fish oils that is responsible**
12:41:03 **for their blood pressure and heart lowering effects in humans.**
12:41:10 Q **You said heart lowering --**
12:41:11 A **Heart rate lowering, I'm sorry.**
12:41:12 Q **We haven't' spent much time with heart rate. Is heart**
12:41:16 **rate connected to cardiovascular health?**
12:41:19 A **Yes, there are study to show that for patients who have**

12:41:22 elevated baseline heart rates, they live in something of a
12:41:26 hyperdynamic state, and over time this does incur injuries to
12:41:35 heart muscle as well as blood vessels.
12:41:36 MR. ELIKAN: I want to turn now PX 386. This is
12:41:39 article by Dr. McLennan that the parties have stipulated to as
12:41:44 prior art in paragraph 68.
12:41:47 THE COURT: Thank you.
12:41:47 BY MR. ELIKAN:
12:41:54 Q What's the title?
12:41:55 A This paper was published in the *European Journal of*
12:42:00 *Pharmacology* in 1996. It is entitled "The Cardiovascular
12:42:02 Protective Role of DHA."
12:42:05 MR. ELIKAN: And can we highlight the second
12:42:07 sentence of the abstract.
12:42:07 BY MR. ELIKAN:
12:42:08 Q What did the author state was the goal of this study?
12:42:13 A They examined the roles of EPA and DHA which are the
12:42:17 principal omega-3 polyunsaturated fatty acids regarded as
12:42:27 candidates for cardio-protected actions.
12:42:27 Q I want to look at the last sentence of the abstract.
12:42:29 What did the authors conclude from the study?
12:42:35 A They conclude that purified omega-3 polyunsaturated fatty
12:42:44 acids mimic the cardiovascular actions of fish oils and
12:42:44 implied that DHA may be the principal active component
12:42:49 conferring cardiovascular protection.

MR. ELIKAN: Now, turning to page 6, I want to highlight a sentence in the left-hand column about nine lines down beginning with "nevertheless."

BY MR. ELIKAN:

Q **What did the authors state here about the relative effects of EPA and DHA on blood pressure?**

A **That the DHA reduced blood pressure more than a combination of EPA and DHA, which in turn reduced blood pressure better than EPA by itself.**

Q **And what's the clear order?**

A **The order is DHA was better than EPA plus DHA, and that EPA plus DHA was better than the EPA by itself.**

Q **Do you recall that Dr. Heinecke testified that LDL-C was the major determinate of cardiovascular risk that a person of ordinary skill in the art would have taken into account when deciding which particular omega-3 fatty acid formulation to pursue?**

A **Yes.**

Q **Do you agree that in evaluating the overall profile of DHA and EPA, a person of ordinary skill in the art would have considered only LDL-C effects and not the other factors related to cardiovascular health that we've been discussing?**

A **Well, as I mentioned, it's very important to perform a comprehensive inventory of all risk factors in patients at risk for cardiovascular disease, and so the more comprehensive**

approach would argue that the DHA would be beneficial for multiple things, you would want to keep it.

Q And would that have been the view of the person of ordinary skill in the art, keep the DHA?

A Yes.

Q And on factors other than LDL-C, which I'm setting aside for the moment, what did the prior art suggest as far as whether DHA or EPA had advantages?

A That the DHA still had outweighing advantages compared to the EPA.

Q Now, let's focus on LDL-C. Do you recall that Dr. Heinecke testified that as of 2008, EPA would offer an advantage over DHA in terms of LDL-C?

A Yes.

Q Do you agree with that opinion?

A No.

Q Did any of the prior art that Dr. Heinecke relied upon suggest that EPA would offer an advantage over DHA in terms of LDL-C in patients with very high triglycerides?

A No.

Q Now, let's talk about patients with triglycerides below 500, those who are not severely hypertriglyceridemic. For those patients, did the prior art as a whole suggest that EPA had advantages over DHA in terms of LDL-C effects?

A No.

12:45:56 Q **Do you recall that Dr. Heinecke testified that in Mori and Kurabayashi LDL-C did not increase in the patients to whom EPA was given?**

12:46:11 A **Yes.**

12:46:11 Q **Taking the prior art as a whole, and again focusing on the patients with triglycerides below 500, did the prior art consistently report that EPA did not raise LDL-C?**

12:46:26 A **It did not.**

12:46:27 Q **Did you review prior art reporting that EPA raised LDL-C in patients with triglycerides less than 500?**

12:46:36 A **Yes.**

12:46:38 **MR. ELIKAN: Let's look at an example. Can we have DX 1961. And this will be -- we can skip to the front page. I'm sorry, the page with the title, page 3.**

12:46:54 **This is 1996 article about Dr. Rambjør that Dr. Heinecke discussed. It's already been admitted, Your Honor, and the parties have stipulated that it is prior art, and that's in paragraph 72.**

12:47:07 **THE COURT: Thank you.**

12:47:07 **BY MR. ELIKAN:**

12:47:09 Q **Let's turn to page 3, which is where we are now, and the first sentence of the abstract. What was the aim of the study?**

12:47:18 A **It was to determine whether EPA or DHA or both were responsible for the triglyceride lowering effects of fish oil.**

12:47:28 Q **Let's highlight the second sentence.**

12:47:30 **What formulations did Dr. Rambjør test in the different arms in this study?**

12:47:38 A **91 percent pure EPA, 83 percent pure DHA, and a fish oil concentrate that was comprised of 41 percent EPA and 23 percent DHA, and then they used an olive oil placebo.**

12:47:58 **MR. ELIKAN: I'm going to go now to page 5 and pull up Table 3. And let's look at the EPA arm. Can we highlight the --**

12:48:06 **BY MR. ELIKAN:**

12:48:08 Q **What is -- what are the number of subjects in the EPA arm?**

12:48:13 A **The EPA arm had 25 persons.**

12:48:17 Q **That's indicated by the N equals 25?**

12:48:20 A **Yes.**

12:48:21 Q **And what was the LDL-C effect on the EPA arm?**

12:48:25 A **In the EPA arm the LDL increased in a statistically significant way from 2.81 millimoles per liter to 2.97 millimoles per liter.**

12:48:42 Q **You testified that the EPA arm in Mori had 19 subjects?**

12:48:46 A **Yes.**

12:48:47 Q **How does the sample size in Mori compare to the number of subjects in the EPA arm in this study?**

12:48:56 A **There are slightly more persons in this at 25 here compared to 19 in Trevor Mori's paper.**

12:49:02

12:49:05 Q **Does this reference suggest, as Dr. Heinecke contends, that it was understood as of March 2008, that DHA, but not EPA, was responsible for raising LDL-C?**

12:49:22 A **No. The results were decidedly mixed.**

12:49:26 Q **Was there prior art that also reported that DHA did not raise LDL-C in patients with triglycerides below 500?**

12:49:36 A **Yes.**

12:49:39 **MR. ELIKAN: I want to go back to DX 1933, the Agren article and to page 8, and I want to highlight the sentence in the left hand column, five lines down from the top, beginning with "no tendency."**

12:49:52 **BY MR. ELIKAN:**

12:49:59 Q **What did Agren report about the effect of LDL-C in the DHA oil group?**

12:50:06 A **That there was no tendency to increase the LDL cholesterol in the DHA oil group in the present study.**

12:50:12 Q **Do you recall that Dr. Heinecke testified that the person of ordinary skill in the art would not have relied on this paper to determine how LDL-C effects are affected by -- I'm sorry. Let me try that again.**

12:50:28 **Do you recall that Dr. Heinecke testified that the person of ordinary skill would not have relied on this paper to determine how LDL-C levels are affected by administering EPA and DHA because it doesn't compare EPA and DHA, and would have instead looked to the Mori paper which did compare them?**

12:50:49 A **Yes.**

12:50:50 Q **Did Hayashi compare EPA and DHA?**

12:50:56 A **No.**

12:50:56 Q **Did Kurabayashi?**

12:50:57 A **No.**

12:51:06 **MR. ELIKAN: One moment, Your Honor. The Court's indulgence.**

12:51:20 **THE COURT: Yes.**

12:51:22 **MR. ELIKAN: Can we go back to the table, please in Rambjør that we were looking at before. It's Table 3 on page 5.**

12:51:34 **BY MR. ELIKAN:**

12:51:39 Q **Was the rise that you mentioned in LDL-C in EPA statistically significant?**

12:51:48 A **Yes.**

12:51:49 Q **I want to turn now DX 1949. It's the 1996 Conquer reference that Dr. Heinecke discussed.**

12:52:08 **And, Your Honor, it's been preadmit, and the parties have stipulated that it's prior art in paragraph 84.**

12:52:13 **THE COURT: Thank you.**

12:52:13 **BY MR. ELIKAN:**

12:52:17 Q **Turning to the left-hand column of page 4, the second sentence of the last paragraph, how did Conquer characterize the effect of DHA supplementation on LDL-C?**

12:52:32 A **They note that,**

"Although no significant alteration was found in the total and LDL cholesterols with DHA supplementation" --

Q What was that again? Can you say that in plain English?

A They did not find that DHA increased either LDL or total cholesterol.

Q And do these references that we've looked at now Conquer and Rambjør, do they suggest that even in patients who aren't severely hypertriglyceridemic, it was understood that DHA but not EPA was responsible for raising LDL-C?

A No.

Q In your work on this case, did you review prior art that observed that there was inconsistency in the reported LDL-C effects of omega-3 fatty acids?

A Yes, counsel.

MR. ELIKAN: Let's go back to DX 1532, Hayashi, and I want to look at the sentence on the third page under Introduction beginning on the 7th line. The sentence begins with the word "data."

BY MR. ELIKAN:

Q And what did Hayashi observe about the data on the effect of fish oils on LDL-C?

A Dr. Hayashi notes that data on the effects fish oils, rich in omega-3 fatty acids, plasma LDL and HDL levels were contradictory in some cases.

12:54:15 **MR. ELIKAN: And I would like to go now to PX 909. This is an article by Dr. Geppert, it's been pre-admitted, and the parties have stipulated to it as prior art in paragraph 55.**

12:54:33 **THE COURT: Thank you.**

12:54:33 **BY MR. ELIKAN:**

12:54:41 **Q Can we turn to page 3. What's the title of the article?**

12:54:44 **A This is paper published in the *British Journal of Nutrition* in 2006 entitled "Microalgal DHA Decreases Plasma Triacylglycerol Glycerol in Normolipidemic Vegetarians: A Randomized Trial."**

12:55:00 **Q So this is 2006, two years before the priority date.**

12:55:03 **A Yes.**

12:55:04 **MR. ELIKAN: Let's go to page 8, the first full paragraph in the left-hand column, and can we highlight the sentence beginning in the 6th line with the words "inconsistent effects."**

12:55:15 **BY MR. ELIKAN:**

12:55:21 **Q What did the authors observe here about the reported LDL-C effects of DHA?**

12:55:28 **A "Inconsistent effects of DHA on LDL cholesterol levels were reported in previous studies. Some investigators found that LDL cholesterol raising effect of DHA or no effect on LDL cholesterol levels."**

12:55:45 Q **So it was inconsistent?**

12:55:45 A **Yes.**

12:55:47 Q **As you said?**

12:55:47 A **Yes.**

12:55:47 Q **Do you recall that Dr. Heinecke testified that the person of ordinary skill in the art would have disregarded Rambjør and Conquer after Dr. Mori published his article in 2000?**

12:55:59 A **Yes.**

12:56:01 Q **Did this 2006 article, six years after Mori, two years before the priority date, cite to both Conquer and Rambjør as well as Mori?**

12:56:12 A **It sure did.**

12:56:13 Q **Is that in the paragraph or the sentence, the long sentence that we were just looking at?**

12:56:18 A **They are.**

12:56:24 Q **Would a person of ordinary skill in the art have looked only at Mori's 2000 paper or instead the prior art as a whole when assessing the relative LDL-C effects of DHA and EPA?**

12:56:39 A **The prior art as a whole.**

12:56:41 Q **In your work on this case, did you review any prior art that surveyed the literature as a whole and drew conclusions about the relative effects of EPA and DHA on lipid effects and other parameters including LDL-C?**

12:56:59 A **Yes, counsel.**

12:57:00 Q **And what was that? What reference?**

12:57:03 A **It's a reference by Clemmons von Schacky.**

12:57:09 **MR. ELIKAN: Let's go DX 1605. This has been pre-admitted, and the parties have stipulated, Your Honor, that it's prior art. That's in paragraph 82.**

12:57:18 **BY MR. ELIKAN:**

12:57:22 Q **Do you recall that Dr. Heinecke testified that von Schacky's a review and a -- I'm quoting now, summary of the author's interpretation of what the literature showed?**

12:57:35 A **Yes.**

12:57:35 Q **Do you agree with him that von Schacky is a review article?**

12:57:40 A **Yes, and review articles do reflect the opinions and the insights of the author.**

12:57:46 Q **And do you agree with him that it is a summary of what the literature showed?**

12:57:51 A **Yes.**

12:57:53 **MR. ELIKAN: An we have page 1, and can we blow up the bottom of the page.**

12:57:57 **BY MR. ELIKAN:**

12:58:01 Q **What was this summary of what the literature showed compiled?**

12:58:04 A **This was published in 2006.**

12:58:06 Q **And I want to direct your attention to Table 1 on page 9.**

12:58:13 **What did the authors provide as a description of Table 1?**

12:58:16

12:58:17 A **This is a summary of the effects of purified EPA and DHA as observed in human studies on a variety of risk factors and only significant differences were considered for the inclusion.**

12:58:32 Q **And the authors note that the table includes arrows?**

12:58:36 A **Yes.**

12:58:36 Q **What do they say the arrows denote?**

12:58:39 A **Well, they are semi-quantitative reflections of the findings from the literature.**

12:58:45 Q **At the bottom of the table under Note, what generally does von Schacky identify as the source of information for the contents of the table?**

12:58:55 A **There are 14 manuscripts noted there, including manuscripts that we have been discussing here at trial today.**

12:59:02 Q **I want to look at what's reported in the table.**

12:59:05 **Based on their review of the literature, what did the authors of this von Schacky reference conclude about the relative LDL-C effects of EPA and DHA?**

12:59:17 A **Both EPA and DHA received a single upward going arrow, meaning that on balance both omega-3 fish oils EPA and DHA increased LDL cholesterol.**

12:59:35 Q **Is there anything in this table that indicates that different effects on LDL-C were obtained with EPA and DHA?**

12:59:44 A **No.**

12:59:45 Q **And looking again at the Note, below Table 1, do the**

12:59:50 authors include among the references they considered Mori?
12:59:56 A Yes.
12:59:56 Q The reference that Dr. Heinecke relied upon?
12:59:59 A Yes.
01:00:00 Q And did Dr. Von Schacky and his co-authors also consider
01:00:06 the Rambjør reference?
01:00:07 A Yes.
01:00:07 Q I want to ask you about some other parameters in this
01:00:11 table starring with triglycerides. What did von Schacky
01:00:17 conclude about the relatives effects of EPA and DHA on
01:00:22 triglycerides?
01:00:23 A Dr. Von Schacky concluded that they both exerted a robust
01:00:27 effect on triglyceride reduction as indicated by two down
01:00:31 going arrows.
01:00:33 Q Does von Schacky suggest that EPA offers some advantage
01:00:38 over DHA in terms of triglyceride lowering?
01:00:40 A No, they have each two down going arrows.
01:00:45 Q And does this table suggest that the only consideration
01:00:49 for assessing cardiovascular and lipid effects is LDL?
01:00:55 A No.
01:00:57 Q Let's look at some of the other factors.
01:01:01 You mentioned that HDL was viewed as --
01:01:07 A Beneficial.
01:01:07 Q -- beneficial. Could we call that cardio-protective?
01:01:11 A Yes, that's good.

01:01:12 Q **Did the authors of von Schacky conclude that EPA would offer an advantage over DHA in terms of effects on HDL?**

01:01:22 A **A little bit open-ended here. He put a question mark next to a horizontal arrow for EPA, which would denote neutrality. He put an upward going single arrow for DHA. But it looks like on balance he agreed with the literature that DHA would increase HDL with something of an equivocal neutral effect with EPA.**

01:01:51 Q **What about in terms of blood pressure?**

01:01:53 A **EPA, neutral. DHA, reduced blood pressure as evinced by a single down going arrow.**

01:02:08 Q **And would the person of ordinary skill in the art in March 2008 reviewing von Schacky and the prior art as a whole, would that person have concluded that EPA offered an advantage over DHA with regard to blood pressure?**

01:02:25 A **No, a POSA would have find a semi-quantitative evaluation of the available evidence very helpful because you can tell by looking, based on number of arrows, directionality of the arrows, what's happening here.**

01:02:41 **And almost at a glance can you look down at this table and go point by point by point, and you would not think that EPA was superior to DHA in terms of the whole package.**

01:02:55 Q **Okay. We talked about some of these factors. In terms of heart rate, what did von Schacky conclude about the relative effects of EPA and DHA on heart rate after surveying**

01:03:07 **the literature?**

01:03:08 **A That DHA had a more pronounced effect than did EPA.**

01:03:13 **Q And in terms of endothelial function, what did von Schacky conclude by about the relative effects of DHA and EPA after surveying the literature?**

01:03:27 **A Yeah, endothelial function is an area of great interest and this is because if the endothelium is getting sick -- and the endothelium is the cell type that lines the inner aspect of all of our arteries.**

01:03:42 **If that cell is getting sick, that patient's cardiovascular system is getting sick, and this would be reflected by, say, capacity to induce dilatation of a blood vessel, just by way of example, cranking down, the expression of inflammatory mediators on the cell type, and actually DHA appears to improve endothelial function neutral with EPA.**

01:04:07 **Q Is that because of the one arrow up for DHA and the sideways arrow for EPA?**

01:04:13 **A Yes.**

01:04:16 **Q I just want to make sure I understand.**

01:04:19 **After reviewing the literature, did von Schacky report that EPA offered an advantage over DHA in any of the parameters considered here?**

01:04:27 **A No, it did not offer an advantage for anything. It was on par for triglycerides, cholesterol and LDL.**

01:04:31 **But for blood pressure, for heart rate, endothelial**

01:04:42

function, and possibly for HDL, DHA appeared to get better -- a better semi-quantitative evaluation.

Q And if the person of ordinary skill in the art read von Schacky, would that person have been led to get rid of the DHA from Lovaza and use high purity EPA instead?

A No, that would not have been a logical conclusion from this.

THE COURT: I think it's good time for our lunch break. Is that why you were looking at your watch?

MR. ELIKAN: I figured I was about to start something new, and I --

THE COURT: Yes. As I note, I have a hearing at 1:30. I'm going to try to limit that hearing to 30 minutes, but, to be safe, let's plan to resume at about 2:15.

I inform you of the emergency issue that we have in the Las Vegas courthouse. I may have to schedule a call this afternoon with the unit executives to see what that situation is. So I'll let you know if I need to recess even earlier than I planned at 4:30.

MR. ELIKAN: Thank you, Your Honor.

(The noon recess was taken.)

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01:05:54 1 **RENO, NEVADA, MONDAY, JANUARY 27, 2020, 2:24 P.M.**

01:05:54 2 **---o0o---**

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02:24:57 4 **THE COURT: Please be seated.**

02:24:58 5 **Counsel, before you resume, I do have to recess today at 3:30 to allow me to address continued court operations at our Las Vegas courthouse, and because I'm cutting two hours short for today, if I need to extend the length of trial for the next two days so that you finish as you expected, I would consider that. I just don't know where we will be at the end of today. But, let's resume for now and I do need to break at 3:30.**

02:25:34 13 **MR. ELIKAN: Understood, Your Honor.**

02:25:36 14 **MR. SIPES: Your Honor, this is Christopher Sipes for Amarin. Mr. Klein -- and I believe Ms. Huttner is the court too -- even with this, I think we would certainly anticipate finishing by Wednesday. And there's a possibility, maybe if we extend, that we could finish on Tuesday, which I think would make no one unhappy.**

02:25:54 20 **THE COURT: That's good.**

02:25:54 21 **MR. KLEIN: This is your last witness?**

02:25:56 22 **MR. SIPES: This is our last witness.**

02:25:58 23 **THE COURT: But will you have witnesses?**

02:26:00 24 **MR. KLEIN: Uh, we have two rebuttal witnesses who may or may not testify depending on how the rest of this**

02:26:03 25

testimony goes.

THE COURT: Ms. Huttner, do you agree with that.

MS. HUTTNER: Yeah. That's fine. There were some other witnesses that had been pulled, so we're fine with that.

THE COURT: Thank you. And if we finish Tuesday, then that's great. I just don't want to inconvenience you all because you thought you were finishing by Wednesday, if the result of me recessing earlier today will affect anyone's schedule. So, that's available it we need to go longer tomorrow or Wednesday.

MR. SIPES: Thank you.

THE COURT: Thank you.

MR. ELIKAN: Your Honor, may I proceed?

THE COURT: Yes.

MR. ELIKAN: A housekeeping issue before I resume.

We were -- at the beginning of my examination I mentioned ATP III, and Your Honor referenced paragraph 41, which is the paragraph in the stipulation which, in the -- of the paragraph addressing, actually, whether the executive summary was prior art. The paragraph relating to ATP III is actually paragraph 64.

THE COURT: Thank you.

THE COURT: That's paragraph 64 for the record

in ECF 324, the Joint Stipulation.

MR. ELIKAN: Yes, Your Honor.

THE COURT: Thank you.

DIRECT EXAMINATION RESUMED

BY MR. ELIKAN:

Q Let's turn back to PDX 6-21. I want to focus now on the third point.

In 2008, was there a finite or limited number of potential options to try to solve the problem with developing an improved treatment for severe hypertriglyceridemia?

A No.

Q Would there have been two or three options?

A No. There could have been hundreds of options.

Q And irrespective of the number of options, was it predictable that you could avoid substantial LDL-C increases by following any of those options?

A No, counsel.

Q And why is that?

A Because, again, the group below 500 behaved differently than the group above 500, and there was no evidence to suggest that any available agent behaved differently when administered to a patient.

Q Is that relating to the mechanism of action of the metabolism that you described earlier?

A Yes.

02:28:37 Q **Let's turn now to the number of options.**

02:28:40 **Would a potential option for a new treatment for severe hypertriglyceridemia have been a new type of fibrate products?**

02:28:49 A **Sure.**

02:28:51 Q **Could the person of ordinary skill in the art have pursued a new type of niacin product?**

02:28:52 A **Sure.**

02:28:57 Q **An entirely new type of triglyceride lowering agent?**

02:28:57 A **Yes.**

02:28:58 Q **Combination of existing agents?**

02:29:02 A **Yes.**

02:29:02 Q **Let's talk now about omega-3 fatty acids.**

02:29:04 **Do you recall that Dr. Heinecke testified that as of March 2008, there were not many options for potential new omega-3 fatty acid formulations?**

02:29:09 A **Yes.**

02:29:11 Q **Do you agree with him?**

02:29:17 A **No.**

02:29:19 Q **What types of options would there have been in terms of composition for a treatment made of omega-3 fatty acids, potentially useful in lowering triglycerides in patients with severe hypertriglyceridemia?**

02:29:20 A **You could have varied the ratio between the two principal omega-3s. You could have varied the dose. You could have**

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02:29:45

also introduced, as some people did, alpha-Linolenic acid. You could have considered adding Omega-6s and Omega-9s. The list was potentially infinite.

Q In turning to dose, would there have been a variety of doses that a person of ordinary skill in the art might have considered had that person wanted to develop a new omega-3 fatty acids formulation for treating patients with severe hypertriglyceridemia?

A Absolutely.

Q As of March 2008, did the medical literature provide a reason not to use a 4-gram dose of an omega-3 fatty acid?

A Yes.

Q Let's turn to PX 567. This is the Nilsen article, "Effect of a High Dose Concentrate of n-3 Fatty Acids or Corn Oil Introduced Early After an Acute Myocardial Infarction on Serum Triacylglycerol and HDL Cholesterol."

It's pre-admitted. And, Your Honor, the parties have stipulated that its prior art in paragraph 77.

THE COURT: Thank you.

BY MR. ELIKAN

Q And in the left-hand column under the heading, Abstract, what does Dr. Nilsen state as the objective of the study?

A He notes the objective was to evaluate the effect of a high dose ethylester concentrate of omega-3 fatty acids administered early after an acute MI or heart attack on

subsequent cardiac events and serum lipids.

Q And looking at the paragraph labeled Design, right below, what does this publication state was the dose of omega-3 fatty acids that was studied?

A Um, they took 300 patients with an acute MI, and randomly assigned them to either 4 grams of highly concentrated omega-3 fatty acids or corn oil, administered in a double-blind manner over one to two years.

Q So was the dose of the omega-3 fatty acids 4 grams?

A Yes.

Q And do the 4 grams offer any benefit, in terms of cardiac events, as compared to placebo?

A No.

Q And later in the article do the authors offer some possible reasons for why a clinical benefit was not observed with the 4-gram dose?

A Yes.

MR. ELIKAN: Let's go to page 5, and I want to turn to the second to last paragraph on the right-hand side, which is in Discussion. And can we highlight, Mr. Brooks, the first sentence.

BY MR. ELIKAN:

Q In that sentence, what do the authors suggest as one possible reason that the omega-3 fatty acid formulation that

they studied did not show a benefit?

A They state,

"It is also possible that the high doses of concentrated omega-3 fatty acids applied in this study exceeded some optimal threshold level, outweighing the beneficial effect, or even leading to an apparent adverse event."

Q Can you break that down and explain that in plain English?

A Sure. So they were surmising that possibly they had exceeded some therapeutic threshold, and now exposed patients to hazard because, perhaps, the dose of fatty acid was toxic in some way.

Q Was this a study of a population with very high triglycerides?

A No.

Q Would the person of ordinary skill in the art, let's say that person wants to develop a new formulation for very high triglycerides, would they have disregarded this warning about passing an of optimal threshold, or would they still want to make sure the drug wasn't causing problems?

A No. They would want to make sure they haven't exceeded some optimal threshold.

Q Let's turn back to PDX 6-22. And the last reason you have on PDX 6-22 is "Objective Indicia of Nonobviousness."

Do some of the objective indicia you have opinions on, relate to the findings of the MARINE trial?

A **Yes.**

Q **And do others relate to the findings of the REDUCE-IT trial?**

A **Yes.**

MR. ELIKAN: And before we address the objective indicia, I want to discuss the legal standards you used.

Can we have PDX 6-23.

BY MR. ELIKAN:

Q **What was the legal standard that you applied?**

A **That a nexus or relationship must exist between the evidence of objective indicia of non-obviousness and the asserted claims.**

A rebuttable presumption of nexus exists when the objective indicia are tied to a specific product whose use embodies the invention disclosed and claimed in the patent.

And finally, objective evidence must be reasonably commensurate with the scope of the patent claims.

Q **Let's talk about objective indicia that relates to the MARINE trial.**

Have you prepared a slide summarizing that information?

A **Yes.**

Q **Can we have PDX 6-24.**

So is the first of these objective indicia relating to the MARINE trial in satisfaction of the long-felt need?

A **Yes.**

Q **Can you briefly explain how, in your opinion, Vascepa satisfied and met the long-felt need?**

A **Well, the national health and nutrition examination survey found that there are about three-and-a-half million people with severe hypertriglyceridemia in the United States. We were in desperate need of a treatment that could lower the triglycerides safely, without raising the LDL cholesterol.**

Q **As of March 2008, had this issue of LDL-C increases been long recognized as a problem?**

A **Yes, counsel.**

Q **And with triglyceride-lowering agents in patients with very high triglycerides?**

A **Yes, sir.**

Q **And did the prior art reflect that concern?**

A **Oh, yes.**

Q **Let's turn back to PDX 1026, the Carlson reference. And could we go to page 7, and the sentence we looked at earlier.**

And Dr. Toth, am I correct that you pointed out this sentence before,

> **"The finding of major clinical concern in this report is the sometimes quite substantial rise in LDL cholesterol"?**

A **Yes. We did highlight that sentence earlier.**

MR. ELIKAN: Can we go to the first page, Mr. Brooks, and if we blow-up the top.

BY MR. ELIKAN:

Q **And this article is from 1977?**

A **Yes.**

Q **So that's more than 30 years before March 2008, right?**

A **Yes.**

Q **Is there other prior art published after 1977 that reflects the concern about the effect of triglyceride-lowering agents on LDL-C and patients with triglycerides?**

A **Yes.**

Q **Let's turn to PX 964.**

And, Your Honor, this is a the Lopid PDR entry. It's been pre-admitted and the parties have stipulated to it as prior art. And that's in paragraph 103.

THE COURT: Thank you.

MR. ELIKAN: Can we pull up page 2 of the Lopid PDR, and I want to look in the right-hand column, item number 2, under Indications and Usage. And I want to zero in on that paragraph, if we can.

Can we make it larger?

Can we highlight the two sentences about midway down the paragraph, starting with "patients with significantly elevated triglycerides."

BY MR. ELIKAN:

Q What does the Lopid labeling say? What does it report in that sentence?

A It states,

"Patients with significantly elevated triglycerides should be closely observed when treated with gemfibrozil. In some patients with high triglyceride levels, treatment with gemfibrozil is associated with a significant increase in LDL cholesterol."

Q So am I correct that this is talking about patients with high triglyceride levels in that second sentence?

A Yes, sir.

Q Would a person of ordinary skill in the art in 2008 have understood that LDL-C increases would be of greater concern in patients with very high triglycerides, or lesser?

A Please state that again.

Q Would a person of ordinary skill in the art understood that LDL-C increases would be an even greater concern in patients with very high triglycerides?

A It would be a greater concern in patients with very high triglycerides.

Q Let's turn to DX1531.

And, Your Honor, this also has been pre-admitted. It's a Harris article. "Safety and Efficacy of Omacor in

Severe Hypertriglyceridemia." And it's also been stipulated to as prior art in paragraph 42.

THE COURT: Thank you.

BY MR. ELIKAN:

Q **Do you recall Dr. Heinecke's testimony that this article studied Lovaza -- here called Omacor -- and reported that administering it to patients with very high triglycerides resulted in an increase of LDL-C of 31 percent and this -- and that this represented a very significant increase in LDL-C?**

A **Yes.**

Q **Do you agree with him?**

A **Yes.**

Q **Is Harris 1997 another example of LDL-C increases associated with triglyceride-lowering agents in patients with very high triglycerides?**

A **Yes.**

Q **Now, we looked at publications from 1977, 1990, and 1997, all reporting issues with increased LDL-C associated with treatment of very high triglycerides. Did this remain a concern as of March 2008?**

A **Yes, because the issue wasn't solved.**

Q **In your opinion, did Vascepa address those concerns and, in the process, meet a long-felt need?**

A **Yes.**

Q **And why is that?**

A **Because it finally solved the issue of reducing triglycerides in a clinically meaningful way in patients with very high triglycerides, without increasing LDL cholesterol.**

Q **Earlier you testified that beyond increases in LDL-C, niacin had severe tolerability issues, and you mentioned flushing and pruritus.**

A **Yes.**

Q **Does Vascepa have those limitations?**

A **No.**

Q **And you mentioned, also, fibrates causing safety concerns.**

A **Yes.**

Q **Does Vascepa raise similar concerns?**

A **No, it does not.**

Q **Do you recall that Dr. Heinecke testified that Mori had already met the need for a triglyceride-lowering agent that did not lead to a substantial increase in LDL-C?**

A **Yes, counsel.**

Q **Remind me, did Mori study severely hypertriglyceridemic patients or mildly hyperlipidemic?**

A **Mildly hyperlipidemic, because the EPA group had a mean baseline triglyceride of 178, while the DHA group had a mean baseline triglyceride of 199.**

Q **And did Mori then meet the need for a triglyceride-lowering agent for severely hypertriglyceridemic**

patients that doesn't substantially increase LDL-C?

A **No.**

Q **You previously testified you're going -- you're relying on Dr. Budoff's testimony that use of Vascepa, according to -- that use of Vascepa according to the labeling satisfies each claim element of the asserted claims, right?**

A **That's correct, counsel.**

Q **And that's -- are you relying on Dr. Budoff's testimony in that regard?**

A **Yes, sir.**

Q **And with that understanding, do you believe there's a nexus between the objective indicia of non-obviousness and the asserted claims, including the meeting of a long-felt need?**

A **Most certainly ly.**

Q **Do you recall did Fisher saying that no drugs have a uniform response?**

A **Yes.**

Q **Do you agree with him?**

A **Oh, yes.**

Q **Were you also in the courtroom when Dr. Fisher testified that to show nexus in this case, you don't need to show that every single patient benefitted from the drug?**

A **Yes. I was here when Dr. Fisher said that.**

Q **If that's the case, does it matter, for your opinions, that some patients in MARINE saw their LDL-C levels rise?**

A **No.**

Q **Or that some patients saw their apo B go up?**

A **No.**

Q **On average, how did patients with triglyceride levels above a 500 respond in terms of their LDL-C? Did the levels go up or down?**

A **On average, they went down just a little bit. And I would say they remained neutral.**

Q **On average, how did patients with triglyceride levels above 500 respond in terms of their apo B? Did it go up or down?**

A **It went down.**

Q **Let's turn back to PDX 6-26, your summary slide on objective indicia relating to MARINE. I want to discuss now unexpected benefits.**

In your work on this case, have you reviewed any publications expressing the view that Vascepa's ability to lower triglycerides and avoid LDL-C increases in patients with very high triglycerides was unexpected?

A **Yes, counsel.**

Q **Let's turn to PX 833.**

What is it?

A **This is an editor's roundtable on hypertriglyceridemia, published in the American Journal of Cardiology.**

Q **And when was it published?**

02:44:52 A **I believe 2013.**

02:44:54 **If we could scroll down.**

02:44:58 **2013.**

02:44:59 Q **And what topic did this publication concern?**

02:45:02 A **Hypertriglyceridemia.**

02:45:06 Q **At the top of the publication, do you see the names of the participants are listed?**

02:45:09

02:45:11 A **I do.**

02:45:12 Q **Who were these people?**

02:45:14 A **Dr. Vincent Friedewald, of the Friedewald Equation; Christie Ballantyne; Harold Bays; and Peter Jones.**

02:45:19

02:45:24 Q **Are they prominent, well-respected doctors?**

02:45:26 A **They are.**

02:45:27 Q **And did you review this article in forming your opinions in this case?**

02:45:30

02:45:30 A **I did.**

02:45:32 **MR. ELIKAN: We'd move for admission of admission of PX 833.**

02:45:32

02:45:37 **MR. KLEIN: No objection.**

02:45:37 **THE COURT: 833 is admitted.**

02:45:37 **(Plaintiffs' Exhibit 833 received in evidence.)**

02:45:37

02:45:39 **MR. ELIKAN: Can we pull up the left-hand column of page 6.**

02:45:41

02:45:41 **BY MR. ELIKAN:**

02:45:42 Q **Do you see a statement by Mr. Harold Bays?**

A **Yes.**

MR. ELIKAN: Can we highlight the last sentence.

BY MR. ELIKAN:

Q **What does Dr. Bays have to say there?**

A **He states,**

"Two surprising results of MARINE were a reduction in serum apo B, and failure of LDL-C to rise."

Q **And in a subsequent response to a question posed by Dr. Friedewald, "why were the apo B and LDL-C results a surprise," how did Dr. Bays explain why he felt there was a surprise?**

A **He notes they were a surprise because prior studies of EPA plus DHA showed little change in apo B. And in patients with very high triglycerides at baseline, EPA and DHA increased LDL-C by as much as 45 percent.**

Q **Do you recall that Dr. Heinecke testified that it was expected that you could lower triglycerides without increasing LDL-C?**

A **Yes.**

Q **I'd like to pose a similar question to the one that Dr. Heinecke addressed, but I need you to listen carefully because I'm going to add a clarification at the end the question.**

Was it unexpected that you could lower triglycerides without increasing LDL-C, in patients with very high

triglycerides?

A **Absolutely.**

Q **In March of 2008, was there a preparation of omega-3 fatty acids that had been approved by FDA for severe hypertriglyceridemia?**

A **Yes, counsel.**

Q **And what was that?**

A **That was Lovaza.**

Q **In your opinion, would the person of ordinary skill in the art have formed an expectation about the LDL-C effects in patients with very high triglycerides based on Lovaza or based on Mori?**

A **Based on Lovaza.**

Q **In your opinion, what was the closest prior art to the claimed invention as of March 2008?**

A **It would have been Lovaza.**

Q **And why is that?**

A **Because it, too, was an omega-3 fatty acid formulation, and it was the only omega-3 fatty acid formulation that had been studied in patients with severe hypertriglyceridemia or very high triglycerides.**

Q **Was it also the only omega-3 that had been approved for treatment of severe hypertriglyceridemia, or were there others?**

A **There were no others. It was the only approved**

formulation of omega-3s.

Q And compared to Lovaza, would a person of ordinary skill in the art, in March 2008, have found it unexpected that Vascepa could avoid substantial increases in LDL-C in patients with very high triglycerides?

A Yes, indeed.

Q And would you characterize the avoidance of LDL-C increases with the claimed invention as a mere difference in degree over Lovaza or, instead, as a difference in kind?

A It is right down the middle a difference in kind.

Q And why is that?

A Because it solved the problem. Lovaza did not solve the problem. Lovaza allowed for, in some cases a massive elevation LDL cholesterol. Vascepa neutralized the problem.

MR. ELIKAN: Let's turn back to PDX 6-27. I want to discuss "Praise."

Can we pull up PDX 6-9.

BY MR. ELIKAN:

Q And you'll recall earlier we discussed these references, the Fialkow and Castaldo references?

A Yes.

Q In your opinion, are these references examples of praise for Vascepa's ability to lower triglycerides in patients with very high triglycerides without substantially increasing LDL-C?

A **Yes.**

Q **And we discussed the O'Riordan article earlier, in which doctors Nissen, McGuire and Bays all expressed enthusiasm for the MARINE trial results, right?**

A **Yes.**

Q **Now, Dr. Heinecke disputes that this is praise for Vascepa. Do you agree with Dr. Heinecke?**

A **No.**

Q **Do you believe that the initial caveats that Dr. Nissen expressed, eliminate his statement that Vascepa gives you all the benefits -- all the benefit without the downside?**

A **Dr. Nissen would never say that if he didn't mean it. Yes, he meant it irrespective of the caveats.**

Q **Let's turn now to apo B.**

Earlier we were looking, a couple minutes ago, at PX 833. And I want to turn back to the statement we were looking at. And I want to highlight again Dr. Bays' answer, the first answers, "two surprising results."

And Dr. Toth, is he also expressing surprise about the reduction in serum apo B?

A **Yes.**

Q **And did he explain in the subsequent response why Vascepa's reduction in apo B was a surprise?**

A **Because prior studies looking at EPA plus DHA showed little change in apo B.**

Q **In your opinion, would the person of ordinary skill in the art, in March 2008, have found it unexpected that EPA would reduce apo B?**

A **Yes.**

Q **As of March 2008, did the prior art report that Lovaza decreased apo B in patients with very high triglycerides?**

A **No, counsel.**

MR. ELIKAN: Let's turn to PX 939.

And this is the Lovaza statistical review that we looked at before.

Can we pull up page 25, Figure 7.

BY MR. ELIKAN:

Q **What data is displayed in this figure?**

A **Counsel, you're looking at the studies from Europe, as we described earlier during testimony, as well as the two studies from the United States. In the European studies, the triglycerides were under 500. In the United States, the mean was, I believe, 812. And we are looking at box plot displays of the data.**

Q **What are box plots?**

A **Box plots allow you to see all of the data in a study. It shows you the dispersion of your patient findings. And the box shows you the so-called interquartile range, the patients who fall between the 25th and 75th percentile of the results.**

Q **I want to focus on what happened in the US studies.**

Those which concern patients with very high triglycerides.

Mr. Brooks, will you blow that up.

Do you these box plots on the right, that we've now blown up, show that Lovaza decreased apo B compared to placebo?

A **No, counsel. What you're looking at on the Y axis is percent change in apo B. And the mean apo B increased between the placebo and the Lovaza treatment arm.**

Q **And how can you tell that?**

A **Because you see a line with a positive slope extending between the mean of the two groups.**

MR. ELIKAN: Your Honor, it had been my intention that he would show where that is using his device, which I understand is not fully functional.

Would it be okay for him to walk over to this screen, perhaps, and show you?

THE COURT: Yes. I didn't realize that the device is not functional.

THE CLERK: As soon as they turn it on, it turns off the television.

THE COURT: All right.

Dr. Toth, would you like to show us on --

THE WITNESS: Sure. Of course.

MR. ELIKAN: Could I turn the screen slightly so that -- unless Your Honor can already see. Whatever you'd

prefer.

THE COURT: I can see. And if anyone in the courtroom would like to see and they need to move from where they're seated, then they should feel free to do so.

THE WITNESS: Can you see?

THE COURT: Miss Clerk, is going to give you the handheld microphone.

THE WITNESS: Can you see?

THE COURT: Yes.

THE WITNESS: Okay.

So what is happening here is you're looking at percent change in apoprotein B. And you see that the mean value of apoprotein B increased in the Lovaza treated group.

BY MR. ELIKAN:

Q And can you point out the line that you mentioned with the slope?

THE WITNESS: It's right here (indicating).

THE COURT: I'm sorry. Let me move over.

Could you show that again.

MR. ELIKAN: Could you maybe --

THE WITNESS: It's this line --

MR. ELIKAN: Dr. Toth, if you'd step over the other side.

THE COURT: I think I'm just not able to see because you were blocking the view.

02:55:17 THE WITNESS: Yeah. This line (indicating). It's upward sloping.

02:55:19 THE COURT: Thank you. That's what I thought.

02:55:20 Thank you.

02:55:22 BY MR. ELIKAN:

02:55:40 Q So, am I correct in understanding then that the K85 arm, Lovaza, there's a reduction in apo B?

02:55:46

02:55:50 A No. It's an increase. Apo B increased.

02:55:54 Q I'm sorry.

02:55:56 Dr. Toth, in which arm did it increase?

02:55:59 A In the K85.

02:56:00 Q Okay. K85 is the --

02:56:03 A Lovaza.

02:56:04 Q Okay. And in your opinion, is this difference between Lovaza and Vascepa one of degree or one of kind?

02:56:25

02:56:29 A One of kind.

02:56:30 Q And why does apo B matter?

02:56:33 A Because it, too, is a predictor of cardiovascular risk.

02:56:40 Q Why? What does it indicate?

02:56:43 A It represents the total burden of what we call atherogenic lipoprotein in serum.

02:56:47

02:56:52 Q Do you recall that Dr. Heinecke testified that the Vascepa results would have been expected over Kurabayashi and Grimsgaard, which administered EPA to patients with mean triglyceride levels below 150.

02:56:57

02:57:05

02:57:09

Do you recall that testimony?

A I do.

Q Do you agree with him that a person of ordinary skill in the art would have looked to those studies in forming an expectation of -- about the effect of EPA in persons with very high triglycerides?

A They could not possibly have done that.

Q Would they have looked, instead, to approved treatments?

A Sure.

Q Like that?

A Yes.

Q Does -- I want to turn now to the REDUCE-IT trial.

In your opinion, do the findings of REDUCE-IT give rise to additional objective indicia of non-obviousness?

A Oh my, yes.

MR. ELIKAN: Okay. Can we have slide PDX 6-28.

BY MR. ELIKAN:

Q In your view, was there a long-felt need for a triglyceride- lowering agent that could lower residual cardiovascular risk beyond the reduction and risk provided by statins?

A Absolutely.

Q And why is that?

A Because we know from studies from around the world that elevated triglycerides increase risk for cardiovascular

events. We also know from some post-hoc analyses from prospective randomized trials -- but let's take the example of the PROVE-IT trial, that even if a patient is aggressively treated with a statin, if their triglyceride is still high, their risk is substantially higher than a patient who is treated with a statin, but their triglyceride is normal.

Q So would you still want to get the risk down a good bit lower?

A Oh, yes. Always.

Q As of March 2008, had the prior art recognized that patients with elevated triglycerides were at increased risk of cardiovascular disease?

A Yes.

MR. ELIKAN: Can we have PX 846.

And, Your Honor, this is a 1998 article by Austin and co-authors, "Hypertriglyceridemia as a Cardiovascular Risk Factor." It's been pre-admitted. And the parties have stipulated to it as prior art in paragraph 79.

THE COURT: Thank you.

BY MR. ELIKAN:

Q Looking at the first sentence of the body of the article, in the left-hand column on page 1, what does this report about the relationship between elevated triglycerides and the risk of cardiovascular disease?

A The paper notes elevated levels of plasma triglyceride

have long been associated with an increased risk of cardiovascular disease.

Q **So even in 1998, it was long -- it had long been associated with an elevated risk of cardiovascular disease?**

A **Yeah. This would go back into the '60s. Yes.**

Q **As of March 2008, for how long had researchers been studying whether triglyceride-lowering agents could lower cardiovascular risk?**

A **At least 30 years.**

Q **To 1978?**

A **Sure.**

Q **In your opinion, why had the question of whether triglyceride-lowering agents could lower cardiovascular risk been studied for so long?**

A **Because people were unable to demonstrate reductions in risk against a statin background, with drugs that impact triglycerides.**

Q **And they still would have been interested in getting cardiovascular risk lower?**

A **Oh, they were desperate for a solution. Yes.**

Q **Prior to REDUCE-IT, had any triglyceride-lowering agent been demonstrated to substantially reduce cardiovascular risk over and above statin therapy?**

A **No.**

Q **Let's talk about some of the cardiovascular studies that**

had been done with different types of triglyceride-lowering agents before REDUCE-IT. I want to start with fibrates.

Prior to REDUCE-IT, had researchers studied whether fenofibrate reduced residual risk over and above statin therapy?

A **Yes.**

Q **And with what results?**

A **This was in the ACCORD trial, looking at patients with diabetes. And patients were on a statin background with Simvastatin. And half the group received fenofibrate. The other group received placebo. And they were unable to demonstrate incremental benefit with the addition of fenofibrate on top of the statin.**

Q **And before REDUCE-IT, had anyone studied whether fenofibrate reduced cardiovascular risk in patients who weren't on a statin therapy?**

A **Yes.**

Q **What trial?**

A **That was the FIELD trial. And in the FIELD trial, once again, diabetics were treated with fenofibrate versus placebo. And the FIELD trial failed to meet its primary composite endpoint.**

Q **I want to turn to the gemfibrozil fibrate.**

A **Yes.**

Q **Prior to REDUCE-IT had researchers studied whether**

gemfibrozil would reduce residual cardiovascular risk over and above statin therapy?

A **No, because it was deemed to be too unsafe.**

Q **Let's talk about niacin.**

Before REDUCE-IT, had the question of whether niacin reduces cardiovascular risk been investigated?

A **Yes.**

Q **Did any of those trials report a cardiovascular benefit?**

A **They did not. There were two. One was called Aim High, which looked at patients with established cardiovascular disease. Everyone was on a statin background. They were treated with niacin.**

The study was discontinued because of futility; meaning, the Data Safety Monitoring Board felt that no amount of additional time of treatment would have led to a separation in the survival curves for the study. So, was shutdown.

Then HPS2THRIVE was done in high risk patients against a statin background. And it, too, was negative for its primary composite endpoint.

And in fact, it was unable to demonstrate efficacy for any individual endpoints either. And, moreover, they found that the addition of niacin led to heightened risk for pulmonary and urinary tract infections, as well as increased risk for gastrointestinal hemorrhage.

Q **Do you recall that earlier we looked at an editorial by**

Dr. Kastelein?

A **Yes.**

Q **That referenced a "parade of failed cardiovascular outcome trials of fish oils" before REDUCE-IT with omega-3 fatty acids"?**

A **Yes.**

Q **I want to turn now to that parade.**

Can you turn to PX 936, either in your binder or on the screen?

A **Yes.**

Q **What is it?**

A **This the final report of the OMEGA trial, which was a randomized placebo-controlled trial to test the effect of highly purified omega-3 fatty acids on top of modern guideline adjusted therapy after myocardial infarction, or heart attack. And it was published in the journal *Circulation*.**

Q **Okay. Can you identify PX 961.**

A **This is the results of the ASCEND trial, published in the *New England Journal of Medicine*, entitled "Effects of omega-3 Fatty Acid Supplements in Diabetes Mellitus."**

MR. ELIKAN: And can we have PX 948.

BY MR. ELIKAN:

Q **I'm going to ask you to identify that as well, Dr. Toth.**

A **This is the report of the ORIGIN trial, published in the New England Journal of Medicine. Omega-3 Fatty Acids and**

Cardiovascular Outcomes in Patients with dysglycemia.

Q PX 949, could you identify that please, Dr. Toth.

A This is the report of the Risk and Prevention Study. And this, too, was published in the *New England Journal of Medicine*. And it's entitled, "Omega-3 Fatty Acids in Patients With Multiple Cardiovascular Risk Factors."

Q Can you identify PX 492.

A This is another report entitled, "Omega-3 Fatty Acids and Cardiovascular Events After Myocardial Infarction," which is the report of the Alpha Omega trial.

Q Published where?

A In the *New England Journal of Medicine*.

Q PX 956, what is that?

A This is the results paper of the Su.Fol.Om3 trial, published in the *International Journal of Cardiology* in 2013. And its title is, "Cardiovascular Effects of B Vitamins and/or omega-3 Fatty Acids."

MR. ELIKAN: Can we turn to PX 938.

BY MR. ELIKAN:

Q What is that?

A This is the DO-IT trial, "A Randomized Clinical Trial on Omega-3 Polyunsaturated Fatty Acids Supplementation and All-Cause Mortality in Elderly Men At High Cardiovascular Risk."

And I -- if we could scroll up, it was -- excuse me

-- down. Sorry. It was published in the *European Journal of Cardiovascular Prevention and Rehabilitation* in 2010.

MR. ELIKAN: Can we turn to PX 930.

BY MR. ELIKAN:

Q What is this?

A This is the results of the AREDS2, or age-related eye disease study. It was published in the *Journal of the American Medical Association*. And it's entitled, "Effects of Long-Chain Omega-3 Fatty Acids and Lutein and Zeaxanthin Supplements on Cardiovascular Outcomes."

Q Do all of these publications describe trials on omega-3 fatty acids that were underway as of March 2008?

A Yes.

Q And is that reflected in information in these publications about the study design, and the timing of patient enrollment?

A Yes.

Q Did you consider all of these publications in your work in this case?

A Yes.

MR. ELIKAN: Your Honor, we move to admit PX 936, 961, 948, 949, 492, 956, 938 and 930.

MR. KLEIN: No objections.

BY MR. ELIKAN:

Q Have you prepared a summary slide with pertinent

information from each of these documents?

A Yes. We have a summary slide.

MR. ELIKAN: Can we have PDX 639, please.

THE CLERK: Your Honor, have you ruled evidentiary on the admission of these?

THE COURT: The motion is granted since there's no objection.

THE CLERK: Thank you.

(Plaintiffs' Exhibits 936, 961, 948, 949, 492, 956, 938 and 930 received in evidence.)

BY MR. ELIKAN:

Q By referring to the titles at the top of each column can you explain what information you have on this slide in each column.

A Yes. We have eight prospective randomized clinical trials involving various formulations of EPA and DHA.

Q And you're looking OM3 study publication column?

A Yes the acronym appears with the date -- the year of publication.

In the second column is the date of initiation of trial, and these varied from 1997 to 2006.

Then you have the omega-3 formulation studied in terms of dose and the variation in the ratio of EPA, DHA study to study to study.

You see in the fourth column primary endpoint, none

03:09:47 **the trials were able to achieve statistical significance for**
03:09:52 **their primary composite endpoint.**
03:09:55 **Then in the final column in the most rightward**
03:09:58 **column is percentage of patients on statins.**
03:10:10 Q **Now, the demonstrative identifies the omega-3**
03:10:14 **formulations studied in these different outcome trials right?**
03:10:19 A **Yes.**
03:10:20 Q **In general terms what did these treatments consist of**
03:10:23 **this terms of composition and dose. Are they all EPA and DHA**
03:10:28 **or are there also other things in there?**
03:10:30 A **There are. Every one of these studies used a different**
03:10:34 **dose and formulation. So the dose is very -- anywhere from**
03:10:38 **400 milligrams to 2.4 grams. But you'll also notice**
03:10:42 **significant variability in the ratio of EPA to DHA.**
03:10:47 Q **We'll get to that in a moment. You had mentioned another**
03:10:52 **omega-3 fatty acid about hour ago, an hour-and-a-half ago.**
03:10:55 A **Yes.**
03:10:55 Q **Might have been a little bit less. Is that listed here.**
03:11:00 A **Yes, ALA which is Alpha-linolenic acid.**
03:11:06 Q **And aside from that one formulation do the others all**
03:11:10 **have substantial amounts of both EPA and DHA?**
03:11:15 A **Yes. Variably so, but, yes.**
03:11:18 Q **I want to look at some of these examples of the**
03:11:20 **formulations that were in these studies underway as of March**
03:11:25 **2008.**

What were the relative amounts of EPA and DHA in the formulation studied in the 400-milligram formulation in the Alpha Omega trial?

A **It was comprised of 226 milligrams of EPA plus 150 milligrams of DHA versus two grams of Alpha-linolenic acid versus EPA-DHA at 400 milligrams plus Alpha-linolenic acid at 2 grams combined.**

Q **And what were the relative amounts of EPA and DHA studied in the SUE FALL OM 3 study, five down?**

A **It was a 2-to-1 ratio between EPA and DHA at 600 milligrams daily versus folic acid plus B vitamins 6 and 12.**

Q **What were the relative amounts of EPA and DHA in the omega 3 intervention studied in R and P?**

A **It was one gram of EPA-DHA with the ratio ranging from .9-to-1 to 1.5-to-1.**

Q **On your chart you have R and P. Is that the same or different from risk and prevention which you mentioned a few minutes ago?**

A **That's the same.**

Q **Does this demonstrative indicate that there were only three options, pure EPA, pure DHA and one mixture contained in both?**

A **No, people were struggling to find a formulation that worked. They were varying the amount of EPA to DHA, that**

ratio. They were varying the total dosage daily. People were trying to find their way in the dark.

Q To find a better cardiovascular risk reducing agent?

A Yes.

MR. ELIKAN: Your Honor, we move for admission of PDX 6-29 under Federal Rule of Evidence 10006.

MR. KLEIN: No objection.

THE COURT: PDX 6-29 is admitted.

(Plaintiffs' Exhibit 6-29 received in evidence.)

BY MR. ELIKAN:

Q Now, each of these results were published after March of 2008, right?

A Yes.

Q Did literature published before March of 2008 assess the question of whether omega-3 fatty acids demonstrate cardiovascular benefits?

A Yes.

MR. ELIKAN: Can we turn to PX 848.

And, Your Honor, this has been pre-admitted. It's an article by Dr. Hooper and others, "Risks and Benefits of Omega-3 Fats For Mortality, Cardiovascular Disease and Cancer, Systematic Review," and the parties have stipulated that it's prior art. It's in paragraph 80.

THE COURT: Thank you.

MR. ELIKAN: Can we pull up in the top of the

page and blow it up.

BY MR. ELIKAN:

Q When was this article published?

A This article was published in the *British Medical Journal* in March of 2006.

Q So that's just two years before the priority date?

A Yes.

Q And very briefly and in general terms what did this publication concern?

A This is "A Systematic Review on the Risks and Benefits of Omega-3 Fats For Mortality, Cardiovascular Disease, and Cancer."

Q Are you reading from the objective field?

A I read from the title. But I can read from the objective field.

Q What did the authors state is their objective?

A "To review systematically the evidence for an effect of long chain and shorter chain omega-3 fatty acids on total mortality, cardiovascular events, and cancer."

MR. ELIKAN: Can we turn to the results section in the left-hand column of the first page and highlight the first sentence.

BY MR. ELIKAN:

Q How many studies did the authors say they reviewed for

03:15:35 **their analysis?**

03:15:37 **A Well, they did a comprehensive literature search and**

03:15:45 **identified 15,159 potential studies to include. But based on**

03:15:54 **their inclusion criteria, they whittled it down to 48**

03:15:59 **randomized controlled trials including, 36,913 persons and 41**

03:16:04 **cohort studies.**

03:16:05 **Q What's a cohort study?**

03:16:06 **A A cohort study is a study like the Framingham study in**

03:16:11 **Massachusetts where you identify a group of people and then**

03:16:15 **you follow them out over time and you investigate various**

03:16:19 **issues relevant to health and see how certain features,**

03:16:25 **demographic features, physiologic features et cetera impact**

03:16:30 **risk for specific diseases.**

03:16:31 **Q And how far back in time did some of these 89 trials go?**

03:16:36 **A To 1966.**

03:16:41 **Q In the second sentence of this results paragraph, what**

03:16:44 **did the authors report about the findings of these trials?**

03:16:48 **A That they were inconsistent.**

03:16:50 **Q And then in the following three sentences, what overall**

03:16:54 **observation did the authors draw about the trials on the**

03:16:58 **whole?**

03:16:59 **A They say,**

03:17:00 **"The pooled estimate showed no strong**

03:17:03 **evidence of reduced risk of total mortality or**

03:17:07 **combined cardiovascular events in participants taking**

additional omega-3 fats. The few studies at low risk of bias were more consistent but they showed no effect of omega-3 total mortality or cardiovascular events."

Q **And what in a nutshell does all that mean?**

A **That omega-3s were not found to be beneficial or helpful in terms of reducing your risk of dying, of sustaining cardiovascular events or of developing cancer.**

Q **Let's look at the conclusion field below. What do the authors announce as their conclusion?**

A **That long chain and shorter chain omega-3 fats do not have a clear effect on total mortality, combined cardiovascular events, or cancer.**

Q **The results section that we looked at before, said that studies on cardiovascular benefit had shown inconsistent results?**

A **Yes.**

Q **Before REDUCE-IT were there any studies that reported a possible cardiovascular benefit?**

A **Yes.**

Q **Had any of the trials that reported positive outcomes studied mixtures of EPA and DHA?**

A **Yes.**

Q **Which one?**

A **It would have been just E 3.**

Q And did those cardiovascular outcome trials that did report in reductions in cardiovascular events lead the medical community generally to conclude that omega-3 fatty acids were in fact effective to reduce cardiovascular risk?

A It did not induce a shift in practice, no.

Q Do you recall that Dr. Heinecke testified that in light of JELIS, there was no unmet need for triglyceride lowering agent that reduced cardiovascular risk?

A Do I agree with that?

Q No, I'm asking whether you recall that?

A Yes, I do.

Q Was the JELIS study widely embraced by the medical community as establishing that Epadel was effective to reduce cardiovascular events either alone or on top of statin therapy?

A No, and it did not get approved for that indication here in the United States based on JELIS.

Q Let's discuss JELIS. Very briefly what did JELIS study?

A JELIS studied Japanese patients who some did not have established cardiovascular disease, they were primary prevention and then there were patients who had established cardiovascular disease and they were in the secondary prevention group.

The patients were on very low doses of statins and they were randomized to receive either EPA or placebo and then

followed for just under five years.

Q Let's turn to DX 1553. And this is the 2007 Yokoyama article which has been pre-admitted.

Looking at the tile what the patient group that was studied?

A What was the patient group that was studied?

Q What type of patients?

A As I said both primary and secondary prevention.

Q I'm looking at the title I see a long word hypercholesterolemic.

A I see. I see what you mean.

Q What are hypercholesterolemic patients?

A I'm sorry, counsel. Hypercholesterolemic patients have high levels of cholesterol and typically high LDL.

Q Now, could we pull up the methods paragraph.

A Yes.

Q And I want to highlight the second sentence.

What did Yokoyama state about what pharmaceutical treatments the patients received?

A They were randomly assigned to receive either 1.8 grams of EPA daily with a statin or a statin only. And they were about evenly divided at 9300 patients per group with just under a five-year follow up.

Q I want to go to page 3 and zoom in on Table 1. Do you see the table reports mean serum lipid values including

triglyceride levels for the population studied?

A **Yes.**

Q **And are these reported in millimoles per liter?**

A **Well, the *Lancet* is a British journal so it's in millimoles per liter.**

Q **Do you have a slide that converts the millimoles per liter reported in Yokoyama into the milligrams per deciliter unit of measurement we've been discussing?**

A **Yes, counsel.**

MR. ELIKAN: Can we have PDX 630.

BY MR. ELIKAN:

Q **So converted to milligrams per deciliter, what was the mean triglyceride level of the population administered EPA in JELIS?**

A **153 milligrams per deciliter.**

Q **Was this a study population with severe hypertriglyceridemia?**

A **No.**

Q **How would you characterize the mean level of 153?**

A **A mean level of 153 is just over normal. ATP III defined normal as less than or equal to 150.**

Q **Converted from millimoles to milligrams per deciliter, what were the baseline LDL-C levels of patients receiving EPA in JELIS?**

A **It was remarkably high at 181 milligrams per deciliter.**

Q **I want to look the summary section on page 1. In the first sentence of the paragraph labeled findings, what result did Yokoyama report with respect to the primary endpoint?**

A **A 19 percent relative reduction of major coronary events.**

Q **Have you reviewed subsequent publications that indicate that the JELIS trial did not establish that EPA reduced cardiovascular risk?**

A **Yes.**

Q **Let's turn to PX 953. Can you identify that?**

A **Yes. This is a Cochrane analysis of the impact of omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease.**

Q **What's Cochrane?**

A **Well, that is a very, very respected group of investigators in England who perform meta analyses on a broad range of health related issues.**

Q **Is this a meta analysis?**

A **This is.**

Q **And did you review it in this case?**

A **Yes counsel.**

MR. ELIKAN: We move for admission PX 953.

MR. KLEIN: To objection.

THE COURT: 953 is admitted.

(Plaintiffs' Exhibit 953 received in evidence.)

BY MR. ELIKAN:

Q Please turn to page 66. I want to look at the right-hand column and the section implications for practice.

In the first sentence of the third paragraph, what do the authors of the publication generally conclude about the efficacy of omega-3 fats for preventing or treating cardiovascular disease?

A "That supplemental long chain omega-3 fats are probably not useful for preventing or treating cardiovascular disease although long chain omega-3 fats can help to reduce serum triglycerides and raise HDL a little."

Q This talks about omega-3 fats. Is that the same thing as the omega-3 fatty acids we've been discussing?

A Yes.

Q Did the authors of this publication qualify their statement and say they believed high purity EPA was an exception to the overall assessment of probably not useful?

A They don't.

MR. ELIKAN: Let's turn to page 33 and I want to look in the left hand column. Can we highlight the third sentence.

BY MR. ELIKAN:

Q What does this indicate about whether the meta-analysis included the JELIS trial?

A Well, it shows that it included the JELIS trial.

Q **Did the included studies here, do they include REDUCE-IT?**

A **No.**

Q **Was the meta-analysis that we're looking at published before or after the REDUCE-IT results were announced?**

A **Before.**

MR. ELIKAN: Let's turn to PX 954.

BY MR. ELIKAN:

Q **What is this?**

A **This is another meta-analysis by Aung and co workers published in the fall of 2018 in JAMA cardiology and it's entitled, "Associations of Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks Meta-Analysis of 10 Trials Involving 77,917 Individuals."**

MR. ELIKAN: We move for admission of PX 954.

MR. KLEIN: No objection.

THE COURT: 954 is admitted.

(Plaintiffs' Exhibit 954 received in evidence.)

MR. ELIKAN: Can we have the conclusions and relevance paragraph from page 1 on the screen.

BY MR. ELIKAN:

Q **What did the authors report in their conclusions and relevance section?**

A **They conclude,**

"This meta-analysis demonstrated that omega-3 fatty acids had no significant association with fatal

or nonfatal coronary heart disease or any major vascular events. It provides no support for current recommendations for the use of such supplements in people with a history of coronary heart disease."

Q Did the authors somewhere qualify this statement and say they believed EPA was effective in preventing or treating cardiovascular disease?

A No, counsel.

MR. ELIKAN: Let's go to page 3. And I want to pull up the table titled Characteristics of Included Trials.

BY MR. ELIKAN:

Q And looking at this list, does it include the JELIS trial?

A It does.

Q Did the Yokoyama paper identify how the primary endpoint was defined?

A Yes.

MR. ELIKAN: Let's go back to DX 1553, and I want to pull up the second to last paragraph in the left-hand column on the second page.

BY MR. ELIKAN:

Q How did the JELIS trial define the primary endpoint?

A The primary endpoint was,

"Any major coronary event including sudden cardiac death, fatal and nonfatal myocardial

infarction and other nonfatal events including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting."

Q Does the data in Yokoyama indicate that the overall 19 percent risk reduction was driven by any particular component of the primary endpoint?

A Yes.

Q Which one?

A Unstable angina pectoris.

MR. ELIKAN: Let's look at that. Can we have Figure 3 on page 5.

BY MR. ELIKAN:

Q What's represented in Figure 3, generally?

A Figure 3, like we saw with the REDUCE-IT trial, is showing you graphically how individual endpoints, including the primary composite endpoint fared in terms of statistical significance.

They're showing you the number of events in both the control and EPA group. The P value for significance, the hazard ratio and then the graph shows you how wide the confidence intervals are and where the individual endpoint wound up relative to unity.

Q And what do you mean by unity?

A Okay. That's the vertical line. That's the number 1. If a point falls right on 1, it means it was neither harmful

nor beneficial.

If it's to the left of that vertical line, it implies something that is beneficial as long as the horizontal line doesn't cross 1, and then if it's to the right of unity that means it's harmful.

Q Do you see at the top there's reference to major coronary events?

A I do.

Q Was that the primary endpoint?

A Yes.

Q And to the right of that listing, for major coronary events, what information is displayed here?

A You see the number of people who sustained a major coronary event on the EPA treatment arm which is 262. The number who sustained an event in the control arm, which was placebo, at 324. The P value of .01 which is significant and then the hazard ratio of .81.

Q And what does that mean in terms of relative risk reduction?

A That means a 19 percent relative risk reduction.

Q And you do you see under the label major coronary events there's a line for items of account?

A Yes.

Q And then five different categories are indented?

A Yes.

03:30:48 Q **And what do those five categories underneath items of**
03:30:55 **account, how are those related to items of account?**
03:30:59 A **Well, sudden cardiac death is where you would --**
03:31:03 Q **I'm sorry, I'm not asking what they are, but what's the**
03:31:05 **relationship, if any between those five items and the heading**
03:31:10 **items of account?**
03:31:11 A **Well, they are the individual constituents of the primary**
03:31:17 **composite endpoint.**
03:31:20 Q **And looking at this figure, what, if anything does this**
03:31:25 **data show about the role of unstable angina as a driver of the**
03:31:30 **overall 19 percent risk reduction for major coronary events?**
03:31:35 A **Well, it was the only component of the five constituents**
03:31:40 **that was statistically significant.**
03:31:48 Q **Is unstable angina more or less subjective than other**
03:31:53 **endpoints like heart attack, stroke, cardiovascular death?**
03:31:58 A **It's more subjective.**
03:32:00 Q **Do you recall that Dr. Fisher testified that JELIS was an**
03:32:05 **open label study?**
03:32:07 A **Yes.**
03:32:07 Q **Do you agree with him?**
03:32:09 A **Do you agree that it was open label study, yes.**
03:32:13 Q **Would it have been of concern in an open label study --**
03:32:18 **maybe before going further, what's an open label study?**
03:32:21 A **Open label is where both the investigator and the**
03:32:23 **participant in the trial know which arm that they've been**

assigned to. It's unblinded.

Q Would it have been of concern that in an open label study all the more objective components of the primary endpoint don't show statistically significant outcome difference while the more subjective endpoint did?

A Yes, that's concerning.

Q And why is that?

A Because if a study is not blinded, that does introduce bias. And unstable angina is the most subjective because you don't have a lot of objective features, objective measures to tell you, oh, this patient has unstable angina. They may come in with chest pain but the chest pain isn't necessarily attributable to heart pain or angina. It could be lots of things. And it's up to the physician evaluating the patient as to whether or not they're going to diagnose unstable angina.

But if you know that they are or are not on therapy, that could influence your decision to call it one way or the other.

Q Would a person of ordinary skill in the art as of March 2008 reviewing the data in Yokoyama, have concluded that bias may have played a role?

A Yes. It's been estimated that when you have an unblinded study, you can actually inflate the benefit by up to 17 percent.

03:33:58 Q **I want to turn back to PX 272 -- I'm sorry, Your Honor.**

03:34:02 **THE COURT: I'm trying to find a good time to break because we're past 3:30. But I don't want to interrupt your flow because I know you wanted to go back to the prior document.**

03:34:14 **MR. ELIKAN: Your Honor, I'm happy to stop now, if that's your preference. I'm going to otherwise be going for a good bit before I'm finished with this piece.**

03:34:23 **THE COURT: Then why don't take a break for today. I have a lot of people waiting for me, and I don't want keep them waiting.**

03:34:30 **I do have one curiosity question. And I realize that this is not -- that it may not be relevant and it doesn't appear to be in dispute because none of the experts have pointed this out but I've heard extensive testimony about available therapy before Vascepa including niacin, and one of the adverse effects of niacin is this flushing effect, but I thought that that's been resolved through the no flush niacin, but perhaps one the experts can satisfied my curiosity when we resume tomorrow.**

03:35:04 **MR. ELIKAN: That's fine or perhaps Dr. Toth could allay your curiosity right now if it's okay with you.**

03:35:11 **THE WITNESS: I could do it very quickly.**

03:35:13 **THE COURT: Yes.**

03:35:13 **THE WITNESS: The no flush niacin did not solve**

03:35:16 that issue, it merely substituted what we call NAD or
03:35:16 nicotinamide adenine dinucleotide which is related to niacin,
03:35:27 it can be converted to niacin, but the problem is it wound up
03:35:29 having a lot of liver toxicity so it really never took off.
03:35:33 THE COURT: Thank you. That explains it.
03:35:36 Thank you. We'll resume tomorrow.

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I certify that the foregoing is a correct transcript from the record of proceedings in the above-entitled matter.

/s/Kathryn M. French 2/3/2020
Kathryn M. French, CCR #392, RPR
Official Reporter

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